COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF

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Dedicated

to

my Family

&

Teachers

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Dr. Gaurav Bhatia

ABBREVIATIONS

STSG	Split thickness skin graft
PRP	Platelet rich plasma
GA	General anaesthesia
SA	Spinal Anaesthesia
HAM	Human amniotic membrane
M	Male
F	Female
NS	Normal saline
B	Bupivacaine
SD	Standard deviation
RSA	Road side accident
i.v	Intravenous
VAS	Visual analogue scale

ABSTRACT

Introduction: Skin grafting is a commonly performed surgical procedure for soft tissue defect reconstruction. Split thickness skin graft harvesting creates a new partial thickness wound called the donor site. Donor site pain is one of the most distressing symptoms reported by patients in the early postoperative period.

Aims: To compare the efficacy of 0.125% bupivacaine moistened dressing and conventional dressing for pain relief on skin graft donor sites and report any adverse effects.

Materials and methods: This randomized, prospective, comparative study was conducted at Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital. Sixty patients were randomly divided into two groups with 30 cases in each group. In Group A, skin graft donor site dressing was kept moist with 12 ml/100 cm^2 of 0.125% bupivacaine solution and in Group B, dressing was moistened with same amount of normal saline. Patients with complains of pain or in whom pain score was more than 4 (i.e. need for analgesia), were given intravenous (IV) tramadol. Final conclusion was made after 24 hours.

Results: The two groups were comparable with respect to gender, age, mode of onset, type of anesthesia and donor site area.

In Group A, 5 out of 30 (16.7%) patients required rescue analgesia. In Group B, 27 out of 30 (90%) patients required rescue analgesia ($p < 0.001$). There was 83.3% effectiveness of bupivacaine soaked dressing while only 10 % effectiveness of conventional dressing. Mean pain scores were consistently lower in Bupivacaine group. No significant adverse effects were noted.

Conclusion: 0.125 % Bupivacaine soaked dressing is more effective in pain relief and in reducing requirement of rescue analgesia, in early postoperative period, at split thickness skin graft donor site compared to the conventional dressing.

Keywords: 0.125 % Bupivacaine, split thickness skin graft, donor site, rescue analgesia

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INTRODUCTION

Skin grafting is amongst the commonest methods that have been described for covering skin defects. It's use has been elicited in literature as early as in 1500s by the Germans and Hindus.[1,2] It had gained a wide acceptance and popularity in the nineteenth century, when Reverdin published his account of pinch grafting (1869). This was soon followed by Ollier and Thiersch's accounts of thin split thickness skin grafting (1872 and 1886, respectively), and description of full-thickness skin grafting by Wolfe and Krause (1875 and 1893, respectively). It has, since then, evolved into a reconstructive option which is being routinely used either alone or in combination with various flaps.[3]

Skin grafting is the surgical procedure that is mostly done for soft tissue defect reconstruction. It has a variety of applications making it valuable not only to plastic and reconstructive surgeons but also to various other surgical specialties as well.[4]

Split thickness skin grafts are used in most burns, reconstructive procedures and extensive wound management.[4] They can be applied for resurfacing large wounds, line cavities, re-surfacing mucosal deficits, closure of flap donor sites, coverage of muscle flaps and for tissue loss across joints in areas where contraction will cause a deformity.[5] They also find their great value in achieving temporary closure of wounds that are created by excising lesions requiring pathologic examination before any definitive reconstruction is attempted.[6]

The reliability and relatively a high availability of donor sites in our body for harvesting STSG's make them one of the first choice in reconstructive procedures.[7]

It is the ease of harvesting and application that has made this the preferred option in a varied number of scenarios. Reconstruction with split thickness skin grafts is now one of the most frequently practiced procedures in plastic surgery and has a firm hold as a fundamental step in the emphasized reconstructive ladder.[8]

The advantages of split thickness skin grafting are numerous. Apart from coverage of the area, grafting also leads to a significant reduction in the course of treatment needed (and duration of hospitalization) and an improvement in the functioning and appearance of the area of the body receiving the skin graft.[9]

The skin grafts can be either full thickness or split thickness skin grafts. A split thickness skin graft comprises of epidermis and superficial dermis. It is harvested from a remote area of healthy skin and is then transferred to the excised wound for coverage. After harvesting split-thickness skin graft, a new iatrogenic partial thickness wound is created with some dermal appendages intact. This is called the donor site.[10] This iatrogenic wound and its dressing have posed a big challenge for surgeons in last three decades and still big dilemma persists regarding its management.

STSG ,although being standard of care for full thickness burn wounds and other reconstructive procedures, numerous complications such as impaired healing, infection, excessive pain, scarring, pruritus and either hypopigmentation or hyperpigmentation, are commonly reported on the donor site.[11] Since 1999, veteran's health administration has called for regularly documenting donor site pain as the “fifth vital sign.” In current clinical practice, this vital sign has frequently proved to be much more complex with regards to assessment, evaluation and management. Also being guided by pain as the 5th vital sign mandates, the patients report pain and obviously expect the clinicians to respond. Many clinical practitioners are unaware as to what should be the appropriate response because of lack of education in the approach, examination and thus in overall subsequent management.[12]

Pain is defined by International Association of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”[13]

Donor site pain is also one of the most distressing symptoms that has been reported by patients, especially in the early postoperative period. Donor site creates painful iatrogenic wounds due to exposure of free nerve endings in dermis. The harvest of graft stimulates pain receptors

in the dermis and these pain signals are then transmitted to the central nervous system by afferent fibers in the cutaneous nerves supplying the harvested site. Donor sites from split-thickness skin grafts (STSG) are thus known to impose significant amount of pain on patients especially during the initial post operative days.[14]

Also, larger donor sites are known to stimulate a greater number of pain receptors. Thus, inference can be drawn without any doubt that the amount of pain would be in direct proportion to the size of the graft that is harvested.[15]

Often, the donor site is reported by the patients to be more painful than the recipient site. This pain has a great affect on the post operative course and thus patient's overall recovery. This has significant affect on early mobilization, has reduced sleep, and an increased need for analgesic requirement postoperatively.[16]

Donor site pain is also a significant stressor during hospitalization and this uncontrolled pain in the acute setting is a reliable predictor of developing chronic pain in burn patients.[17] The intensity of this pain is such that it can give rise to many adverse effects such as elevated blood pressure, agitated behaviour and so nullifies the overall treatment goal by impairing the wound healing process. In the immediate post operative period, this pain control is especially difficult and very challenging.[18]

For alleviation of this donor site pain, use of analgesics such as morphine or morphine-like substances is very frequent and that too in higher dosages. Unfortunately, this systemic use of the opioids can cause many adverse effects like nausea, vomiting, pruritus, constipation, urinary retention and more fatal adverse effects such as respiratory depression. The prolonged use of opioids may also produce tolerance to the drug and hyperalgesia. Such complications may eventually cause additional treatment challenges and longer stays in the hospital.[19,20]

Negative Morarity sign denotes that in partial thickness skin graft, the recipient site is more painful than the donor site. This situation is the reverse of what normally obtains, which is that the donor site of STSG

is more painful than the area receiving the graft.[21] The Morarity sign, thus, designates that when split skin donor site is more painful than recipient site , good graft take is less likely.[22]

Although STSG donor sites ultimately heal, when treated with numerous methods given in our literature which range from simple gauze dressings to complex cultured-cell dressings, majority are reported to be very painful for patients. Even after many advancements in this field, most of the surgeons still use the paraffin gauze dressings. Paraffin gauze dressing has been traditionally used for coverage of donor sites worldwide. It's a kind of a semi-occlusive, dry, non-absorbent, adherent dressing. This dressing is very commonly used by most surgeons for donor site coverage but major drawback of such dressing is pain over donor site.

There are many advanced dressings that are available for donor site coverage. Lots of studies have used many different products like honey, green tea extracts, various organic products but the search for ideal dressing for donor site which may cause significant pain reduction is still on. The various products available include fine mesh gauze impregnated with petroleum jelly, polyurethane semipermeable transparent film, hydrocolloids and fibres like calcium alginate.[23]

The STSG donor sites can be treated with a variety of new and traditional dressing materials but their optimal management is still a mystery and there is still no consensus on the ideal management. The optimal STSG donor site dressing should likely be antibacterial and have haemostatic properties, maintain moisture content. It should also be non-adherent to wound bed, aid in epidermal healing process and cause minimal or no discomfort to the patient. In addition, the dressing should be economical to use. Ideally, the properties of the dressing should enable it to remain in place with no need for changing. Furthermore, a major advantage of an ideal dressing should be significant pain relief at the donor site.[24-26]

Despite an abundance of literature on wound dressings, no consensus has been reached on dressings that optimize post harvest donor site pain.[27] Alleviation of donor site pain can be done by a variety of

approaches including continuous local anesthetic infusion, subcutaneous anesthetic injections, application of topical agents, wound dressings and other non pharmacological measures.

Bupivacaine is an anesthetic agent that acts by blocking the nerve impulses transmitting pain sensation to the brain. It is most commonly used for spinal blocks but it also finds its application in local infiltration and for peripheral nerve blocks.[28] So bupivacaine soaked dressing can be a viable option for split thickness skin graft donor site for early post operative pain management and needs research in this aspect.

Thus, this study was planned to evaluate the effectiveness of bupivacaine moistened dressing in reducing donor site pain, in comparison with conventional saline soaked dressing, for patients requiring split thickness skin grafting for reconstruction of various defects and to cover raw areas.

AIMS AND OBJECTIVES

1. To compare the efficacy of 0.125% bupivacaine moistened dressing and conventional dressing for pain relief on skin graft donor sites.
2. To report any adverse effects.

REVIEW OF LITERATURE

Inspite of the frequent usage of local, regional and free flaps in plastic surgery, split-thickness skin grafting still remains an integral part of reconstructive surgery and provides skin cover for soft tissue defects. Skin graft can be harvested from numerous sites in the body. The split thickness skin graft includes epidermis and a variable portion of dermis. This overall process of harvesting split thickness skin graft naturally creates a new iatrogenic wound known as the “donor site”. This donor site heals by re-epithelization of the surface. There is migration of cells from margins of the wound and from the adnexal structures present in dermis. When conditions are favorable, cells migrate into the wound and cover this iatrogenic wound. The process of healing normally takes 16-20 days. The rate of healing is quite variable and is affected by many factors. This donor site of the skin grafts is a source of great pain and discomfort for the patient and causes significant morbidity.[29,30]

In the year 1869, Jacques Reverdin first placed a 2-3 mm epidermal graft over a wound which was granulating. This graft, not only, covered entire wound but in the process also accelerated wound healing.[31]

There were also a few other pioneers in this field who shared their discoveries and the well hidden secret of grafting. Sir Ollier, a French surgeon, first invented the intermediate thickness skin graft. An eminent scientist, Carl Thiersh, stated that for early donor site healing, thin split thickness skin graft harvesting is better and this is now known as thiersh graft. George Lawson was the one who first reported the full thickness skin graft harvesting.[32]

Even after the developments and discoveries in this field, there was a dilemma among the surgeons regarding the use of skin grafts to cover wounds. It was thought that harvesting a graft will lead to formation of two wounded surfaces of roughly the same size.

Otto Lanz, an eminent Swedish scientist, gave a description of the method of meshing of graft and applying one half of it over raw recipient area and the remaining half to cover the donor site. He said

that in this way both the wounds, recipient and donor site, can heal.[33] Still after all these innovations and observations, the surgeons were not using grafting as a preferred technique for wound coverage.

In 1929, Saint Louis scientists Vilray Papin Blair and James Barret Brown first gave a description of the principles and fundamentals of skin grafting and the process of donor site healing. They specifically cleared the rampant false beliefs of practicing surgeons that if there won't be any dermis left over the wound, then the wound is not going to heal. The fundamentals of skin grafting which they described still hold good in today's modern medical practice.[34]

After gaining knowledge about the fundamentals of grafting, the surgeons still had panic about harvesting the desired thickness of graft. The graft was being harvested using razors which was a technically difficult process. After prolonged research, Humby in 1936 invented a simple instrument for harvesting skin graft. This simple instrument had a guard and therefore prevented deep cuts over the donor site. In due course of time, various modifications were done in the knife. Presently, available one is the modified Humby's knife. To meet the growing demand of harvesting skin graft, technically advanced instruments were a need of the hour. During World War II, the increased demand of graft harvesting ultimately led to the invention of electricity driven dermatomes. These dermatomes could harvest skin graft of desired thickness in a very less time.[32]

Split thickness skin graft can be harvested from almost any area of human body. These donor sites have an inherent ability to heal spontaneously but there are chances of scarring, prolonged healing time, pain at site, discoloration of donor area etc. In today's era, donor sites chosen are usually the areas which can easily be covered under clothes or naturally are hidden. Most commonly used donor sites for split thickness skin graft harvesting are thigh, buttocks and trunk. Donor site selection also depends on recipient site for various reasons.[33]

Another fact in selecting donor site is the thickness of skin. Also, skin thickness of same site varies with age and gender. Infants have thin

skin and men have thicker skin than women regardless of location of donor site. Also, a known fact is that skin is thicker on trunk and thighs than on the eyelids or upper limbs. Jeffrey et al did a study to search for the ideal split thickness skin graft donor site in 2014. They gave a detailed account of quality of ideal donor site. They described in terms of a large donor area, its location and ease of access, its firm underlying structures providing strength for harvesting graft, the presence of thicker dermis that will prevent donor site from non healing, a lesser chance of resultant scar formation and which can be easily hidden under clothes. They conducted many cadaveric studies for assessment of thickness of donor site skin of anterior, lateral and medial thigh and eventually confirmed that anterolateral thigh skin is optimal for harvesting a skin graft. The anteriorlateral thigh skin has a thick epidermal and dermal layer which prevents it from morbidities such as scaring, delayed healing and non healing. Also, this site provides a wider area for harvest and is well hidden under clothes. In our modern practice also, thigh is the most commonly used donor site for harvesting the skin graft.[35]

After conclusive evidence regarding the choice of donor site, the next big challenge was the method to address coverage of the donor site.

In past, donor site was kept open and allowed to heal spontaneously. But such practices have been abandoned long back and nowadays this open technique is not used in practice. Every surgeon now prefers closed dressing over open dressing.[36]

Closed dressings clearly outweighed the open technique. Closed dressings are associated with a short healing time, a low infection rate with regenerated epithelium having a superior quality and ultimately thus have an enhanced patient comfort. With open dressings, there are high chances of donor site desiccation, mechanical trauma causing further injury and higher rates of contamination. Thus, closed dressings are the preferred choice in our practice today.[37]

Zohungha et al did a study and compared histological, histo-chemical and electro-microscopic features in moist and Vaseline gauze dressing to observe the effect of occlusive environment on wound healing of the

skin graft donor site. They found that wounds healed faster under an occlusive moist environment. The inflammation was more serious at the early stage of wound healing and the macrophages appeared earlier. They ultimately arrived at the conclusion that wound of a skin graft donor site in an occlusive moist condition would heal faster than that covered with conventional Vaseline gauze.[37]

The dressings have also been categorized according to the environment around donor site. Dressings can be moist or non- moist. Since many decades research over this topic was in progress and evidences regarding better wound healing with moist dressing are there.

In his meta-analysis, Wiechula compared moist dressings to non moist dressings. He evaluated 58 randomized control trials and intra individual studies where the efficacy of the dressing was determined by documenting signs of infection, its effect on healing, and Visual Analogue Scale scores. He found moist dressings decreased the days needed for healing and were associated with decreased infection and lower pain scores. When comparing differences between the moist dressings, he found hydrocolloids superior to other moist dressings in wound healing and infection. He did, however, find that pooling of results was challenging because a variety of pain measurements were used.[38]

Voineskos et al. also reassessed moist versus non moist dressings by evaluating 75 studies for the same parameters (infection, wound healing, pain). In contrast to Wiechula, Voineskos et al. did not find evidence supporting moist dressings for reducing infection rate. Eleven studies favored moist dressings, five favored non moist, and 14 studies found no differences in wound healing. No dressing category or type was found to be superior. Pain scores were recorded in 58 of the 72 articles and a significant majority used VAS. Regardless of study design and consistent with Wiechula's review, majority of moist dressings were associated with less pain. Voineskos did, however, report that studies reviewed were of low methodological quality. Ultimately, there was a lack of definitive evidence favoring a particular

dressing. Voineskos et al. suggested that future studies should clearly define their experimental parameters and assess outcomes on more standardized scales.[27]

A study done in 2004 by Zhang et al also concluded that occlusive moist dressing environment heals faster than the dry dressing. This was due to fibroblast becoming more active. So, it was hypothesized that moisture in donor site environment helped in migration of macrophages which was important in inflammatory phase of wound healing.[39] So dressings which keep environment moist have been associated with better wound healing and less pain at donor site.

STSG donor site is associated with many problems like pain, fluid loss, prolonged healing time and immobilization, hypertrophic scaring and undesirable pigmentation.[40] Donor site pain and impaired healing are the most disturbing complications. Various type of techniques or dressings have been described and extensive research has been done in this regard to eliminate such potential complications. Thus, aim of such dressings and techniques was to reduce pain and optimize healing of donor site.[11]

A variety of materials have been used for donor site dressings like paraffin gauze, polyurethane, collagen sheets, alginates, hydrocolloids, semi occlusive fabrics, skin graft and biological dressings etc.[41] Different studies have used different dressings but nothing has been proved as the ideal dressing for donor site. A better dressing is the one which promotes wound healing by removal of excess exudates, allowing gaseous exchange and thereby increase the healing rates. It should be also be cost effective with ease of application. Also, another major characteristic should be reduced or absent pain at donor site.[16,27,38]

Donor-site pain following skin grafting is certainly a significant problem in plastic surgery. Although donor-site pain may cause serious patient discomfort, this problem is scantily addressed in the literature. Numerous studies addressing dressing materials mostly focused on improved and rapid donor-site healing and many addressing pain as the other outcome. However, A myriad of topical solutions, dressings,

and other procedures have been described in the literature for donor site pain relief with none providing ultimate solution to this problem.

Traditionally paraffin gauze dressing has been used for coverage of donor site. It is a semi occlusive dressing and has no absorbent properties. Paraffin gauze is prepared by dipping the fine meshed gauze into liquid paraffin and this is stored in a tray. This gauze is then sterilized and used for dressing the donor area. This is most commonly used dressing. Paraffin gauze provides an occlusive environment around the wound and also is believed to help in pain free removal of dressing. This dressing also keeps the area dry. Thus, it is a kind of semi occlusive dry dressing. The major drawback of such a dressing is more pain at the donor site.

In 2013 F.E. Brolmann et al published their work with a conclusion that Vaseline gauze dressing for donor site should be discontinued as it causes more infections at the donor site, apart from being painful.[11]

A novel dressing that has been described in our literature for donor site is the collagen dressing. Collagen dressing is actually a collagen sheet which is developed from bovine collagen and is almost similar to the human collagen in composition. This similarity assumes a great significance and leads to an easy acceptance by body. Thus, rejection rates of these collagen sheets are less. The extracted tissue is treated with various chemical procedures for commercial preparation of such sheets.[42] After chemical procedures, tissue also goes through the enzymatic treatment for formation of a readily usable collagen sheet for human beings. The sheets also then undergo chemical cross linking and after sterilization are packed.

The collagen causes significant increase in the fibroblast production and is hydrophilic in nature, a property that may be important in encouraging fibroblast permeation. It also enhances the deposition of oriented, organized collagen fibers by attracting fibroblasts and causing a directed migration of cells which aid in the uptake and bioavailability of fibronectin. It also assists maintaining the chemical and thermostatic microenvironment of the wound.

Main chemical treatment which is done is deamidation of the bovine tissue so that it becomes more soluble and chemically inert.[43] Such chemical treatment leads to less rejection rates.

There are various biological and physiological properties of these collagen sheets which make them one of the best options for dressing of the wound sites. It is a biological dressing, is non-inflammatory, has a low antigenic potential and undergoes minimal biodegradation ensuring longer shelf life. It helps for better and organized cell migration like fibroblast for a better wound healing.[44]

Collagen sheets also cause less scaring. The physiological properties make it impermeable to bacterial migration. So it acts as a barrier for bacteria and prevents infection. Collagen sheet has elasticity, is easily moldable allowing application over various surfaces and is known to have a good tensile strength but needs to be handled with care while application.[45] It also has been considered pain free while removal.

P Halankar et al in 2005 studied the effect of collagen sheets on donor site dressing. They concluded that absence of the donor site pain and lesser requirement of analgesics in patients was the greatest benefit of this dressing.[46]

In 2015, Sreekumar N.C. et al did a comparative study of the bovine type I collagen dressing with paraffin gauze dressing on skin graft donor site in 20 patients. One-half of the donor site was covered by collagen sheet. Paraffin impregnated gauze was used for covering the other half. They noticed that the pain was less in the collagen area when compared to the paraffin gauze area. The difference in pain scores was greatest in the first 3 days. So, it was concluded that Bovine type 1 collagen dressing reduces pain and soakage at skin graft donor site and has a minimal effect on the epithelization rate.[47]

Polyurethane dressings are another armamentarium in our kit for donor site dressing. These are foam dressings and available as adhesive or non-adhesive type. The commonly used is non-adhesive type. These promote moisture in wound environment and absorb exudates and debris from the wound. The microspores present in the dressing retain the exudates while the semi-permeable membrane allows vapours to

come out. These properties help in early and optimal wound healing. The self-adhesive property of foam dressing has been demonstrated and has been shown as the least traumatic dressing.[48]

In 1995 Weber RS et al from Hauston, USA concluded in their study that absorbent polyurethane dressing foam appears to have potential advantages over petroleum gauze dressing. It produced less initial patient discomfort and has tendency to cause more complete donor site healing by post-operative day 14th.[49]

Garcia- Salinas et al published their study in 2015 which was aimed at assessing the efficacy of non adherent polyurethane dressing in pain reduction and the effect of such dressing on rate of epithelialization at STSG's donor site. They included fifteen patients in their study. They divided the donor sites randomly into two halves in 10 patients. The coverage was done with the non-adherent polyurethane dressing or standard non-adherent gauze. In remaining five patients who had bilateral donor sites, the non-adherent polyurethane dressing was used to cover one side and non-adherent gauze for covering the other side. Assessment of pain was done using a Visual Analog scale.

They found out that postoperative pain showed a significant decline with the non-adherent polyurethane dressing during the length of study.They noticed no effect on epithelialization. So, they arrived at the conclusion that significant reduction of pain is achieved by non-adherent polyurethane dressing in the skin-grafted donor sites, without having an affect on epithelialization.[50]

In 2009 another study, for evaluating polyurethane dressing on 40 patients, done by Cigna E of La Sapienza University, Rome was published. They conducted the study to investigate the possible effects of inclusion of ibuprofen in polyurethane dressing foam for managing pain and healing at split-thickness skin graft (STSG) donor sites. They focussed on using a foam dressing, Biatain-Ibu. This dressing was a combination of absorbent hydrophilic polyurethane foam, Biatain, and had ibuprofen, as active ingredient. The first group of 20 patients had donor sites covered using Biatain-Ibu foam dressing. In 20 patients comprising the second group, the donor site coverage intra-operatively

was done using standard dressing, which had no known agent that could promote healing. The study results thus clearly demonstrated that the use of ibuprofen with bio-occlusive dressings had shown acceleration in wound healing on comparison with fine-mesh gauze dressings. It also almost eliminated pain and discomfort in the patients. They however noticed that itching posed a major problem in the patients who received topical ibuprofen.[51]

Another dressing material used is Alginates. Alginates are produced from the calcium and sodium salts of alginic acid which is found in brown seaweed (Phaeophyceae). The alginate dressing has an inherent ability for fluid absorption and can absorb fluid up to 15 to 20 times its weight. This property is of great benefit in highly exudative wounds.

A prospective randomized study was done by Dominik Kaiser et al which compared the effectiveness of an alginate dressing covered by transparent polyurethane film with a paraffin gauze dressing on STSG donor site. They observed no significant difference in pain and healing time between alginate/polyurethane film dressing and non adherent paraffin gauze. So, they concluded that there were no advantages of using semi-occlusive dressings with alginate and polyurethane film over paraffin gauze. Also, lower costs and having better patient acceptance made paraffin gauze dressings as favoured treatment option for STSG donor sites.[52]

The study done by Dornseifer et al in 2008-2009 compared the modified polyurethane dressing and Aquacel, a hydrofiber wound dressing. They perforated the polyurethane dressing to permit controlled leak towards a second absorbant dressing. Skin graft donor sites were divided equally for applying aquacel and polyurethane dressing. It was observed that polyurethane dressing was significantly less painful until and during removal of the dressing.[29]

Another study was done by Higgins et al in 2012 comparing the calcium alginate and polyurethane foam dressing. It was a randomized controlled trial and ultimately concluded that there was no significant

difference observed between both dressings in parameters pertaining to pain, healing of wound and duration of hospitalization.[53]

Yemer Demirtas did a prospective clinical trial to compare five different dressings for managing the split thickness skin graft donor sites. They used hydrocolloid dressing, Aquacel Ag, polyurethane film, cellulose based dressing and tulle gras for donor site management. Their trial concluded that the hydrocolloid dressing was the best in reduction of pain at the donor site and was most economic amongst the materials.[8]

Another study was done by Lohsiriwat et al which compared the ionic silver-containing hydrofiber dressing and paraffin gauze dressing. They concluded that ionic silver-containing hydrofiber dressing reduces STSG donor site pain and promote reepithelization when compared to paraffin gauze dressing.[54]

Further researches still continued for development of a donor site dressing which could provide adequate pain relief. Hasatsri et al made an innovative bilayered wound dressing which was made of silk and gelatin. This bilayered wound dressing was composed of a wax-coated silk fibroin woven fabric as a nonadhesive layer and a bioactive layer sponge consisting of sericin and glutaraldehyde cross-linked silk fibroin/gelatin. Silk fibroin and gelatin solutions, mixing ratio 20:80, were mixed with 1% w/w sericin solution. So a final solution concentration was obtained at 4% w/w and then crosslinkage done with glutaraldehyde. Gamma irradiation was used for sterilization.The study was conducted to evaluate the safety and efficacy of this innovative dressing for donor site. It was observed found that donor sites which were managed with the bilayered wound dressing had significantly less amount of pain and better healing than those managed with bactigras.[55]

An ethyl alcohol-precipitated silk sericin/Polyvinyl alcohol scaffold which provided a controlled release of silk sericin had previously demonstrated an efficient wound healing in rats. The study by Siritientong et al aimed to further evaluate the clinical potential of this scaffold and named it as “silk sericin-releasing wound dressing”, for the treatment of split thickness skin graft donor sites . They compared this

wound dressing with bactigras and the study results showed that wounds receiving treatment with the silk sericin-releasing wound dressing showed early healing and a significant reduction in donor site pain on comparison with Bactigras.[56]

The search for a dressing which reduced donor site pain had already led to new innovations. Trials persisted with known products having different usage.

One such substance was Nitrofurazone soaked fine mesh gauze, which had demonstrated moist-healing, antimicrobial properties and non-adherent properties. However, there was a lack of research on human studies assessing nitrofurazone soaked fine mesh gauze for STSG's donor site dressing. So study was conducted by Seyed Esmail Hassanpour et al comparing three different methods of dressing for partial thickness skin graft donor site In method A, Paraffin fine mesh gauze was used, Method B used Nitrofurazone soaked fine mesh gauze and in method C, a dry fine mesh gauze was used for split thickness skin graft donor site dressing. Results showed that method B had least severity of pain. They arrived at a conclusion that dressing the donor site with nitrofurazone ointment soaked gauze had lowest complications.[57]

Tanaka et al conducted a prospective study between October 2012 and May 2013 at Department of Plastic and Reconstructive Surgery, Nagasaki, Japan. They tested the donor site wound healing with a non adherent petrolatum and hydrocolloid impregnated polyester, a lipid colloid dressing, and a non adherent polyester dressing, supplemented with petrolatum manually. They observed that re epithelialization was better in lipid colloid dressing. Also, a significant reduction in degree of pain was noted in lipid-colloid dressing as compared to the polyester dressing.[58]

Vitamin E has been known to maintain the integrity and stability of intracellular membrane. It has anti-oxidative and anti-inflammatory properties. But only the acetate form is stable for use topically. Additionally, α-tocopherol acetate (α-TA) shows a reduction in local bacterial growth by lowering the pH.

In order to reduce patient distress at donor site, Stanizzi et al designed and performed a prospective study. In 30 patients, daily dressings were done with α-tocopherol acetate oil and moist gauzes. In other group of 30 patients, dressings were done every 4 days with α-tocopherol acetate oil and silicone–vitamin E gauzes. They observed a significantly lower pain score with α-tocopherol acetate oil and silicone–vitamin E gauzes. Where both type of gauzes could be tested in same donor site area, few patients refused the traditional gauzes as a reduction of pain was experienced in area treated with silicone gauze. They, thus arrived at conclusion that α-tocopherol acetate oil and silicone–vitamin E gauzes led to a significant pain reduction during dressing changes.[59]

Fibrin sealant has shown to lower the time to achieve hemostasis at wound sites. Incidentally, it was observed that patients receiving this treatment had less pain. Fibrin sealant seals the wound and provides occlusive environment. Occlusive dressings prevent exposure of free nerve endings to air. They also reduce the oxygen concentration in wound and so decrease arachidonic acid metabolites, which are also believed to play a role in aggravating pain.[8]

So, the study was conducted by Healy et al b/w 2008 and 2009 which aimed to evaluate pain at split skin graft donor sites in patients who received treatment with fibrin sealant and those without fibrin sealant. Forty patients were included in the study analysis. The self reported pain and incapacity scores were completed by the patients. Twenty received the fibrin sealant plus self-adhesive fabric dressing and 20 received the fabric dressing only (controls). It was observed that patients in which the fibrin sealant plus the dressing was used showed significantly less pain and incapacity. The authors ultimately concluded from the study that the patients in whom split skin graft donor sites were dressed with fibrin sealant plus self-adhesive fabric dressing experienced significantly less pain and incapacity than patients with self-adhesive fabric dressings alone, allowing a more rapid return to normal activity.[60]

Extensive investigations have been performed to study the effects of oxygen on wound healing process. Oxygen finds its importance in angiogenesis, synthesis of collagen, promoting wound contraction, epithelialization, and prevention of infection. All the above listed functions are necessary for tissue repair and wound healing.[61]

Acceleration of healing process and pain reduction during this phase are beneficial. There is early return to daily routine, decreased wound infection, better quality of life, and possibly reduced analgesic requirements. A clinical study done by Kimberly F. Lairet assessed the effectiveness of a new oxygen-diffusion dressing (OxyBand) and compared that with standard Xeroform gauze dressings(3% bismuth tribromophenate and United States Pharmacopeia petrolatum on finemesh gauze) to treat skin-graft donor sites in burn patients. OxyBand is multilayer dressing prefilled with high levels of oxygen between the layers. The top layer forms a barrier film and holds oxygen over the wound, while the bottom layer that is attached to the wound is high transfer-rate film. The dressing acts like an oxygen reservoir. Its purpose is to allow the wound to use as much oxygen as needed, and to supply oxygen on demand. The dressing of one donor wound was done with OxyBand and other with Xeroform gauze. The mean time for wound healing was less with OxyBand. Lower pain scores were observed at the OxyBand site as compared with the Xeroform site. This study thus showed faster healing and reduction in pain at donor sites dressed with an oxygen-diffusion dressing.[62]

Another method described in the literature for donor site pain relief is the use of platelet rich plasma. Currently, clinical research with regard to PRP therapy is focused on wound healing and rate of epithelialization at graft donor sites. Reduction in pain is typically only mentioned secondarily and that too pertains to dressing changes, or in the acute trauma. The platelet concentrate is extracted from patient blood via plasmapheresis.[63]

This extracted plasma is then activated to a gel like substance. This gel like substance consists of a fibrin matrix scaffold with platelet release contents and multiple growth factors. The platelets degranulation

occurs by proteins such as thrombin. This process initiates the release of different growth factors such as platelet-derived growth factor-AB, transforming growth factor beta-1, and vascular endothelial growth factor.[64] These growth factors are considered responsible for faster rate of epithelialization and pain reduction at wound sites.[65]

A pilot study conducted by John D. Miller et al observed a reduction in donor site pain in patients treated with PRP over skin graft donor site. There was a reduction in postoperative narcotic use and better healing, cost effectiveness and no adverse effects. On this basis, PRP was suggested as a beneficial adjunct to reduce donor site pain following STSG harvest.[66] However, it involved use of a time and labour oriented invasive process of harvest and cumbersome apparatus.

The use of human amniotic membrane (HAM) has been reported in literature over hundred years ago for burn and wound management.[67,68] The objective of these early attempts was achieving a durable wound coverage. Although it was ultimately rejected, observations of lack of infections and alleviation of pain were there.[69]

Since past decades, the advantages of amnion as a temporary dressing have become more evident.[70,71] Since the early 1990s, an increasing body of literature exists which addresses amnion use in chronic wounds .

The HAM has proven properties as biological temporary dressing. These include promoting epithelialization and wound healing due to the growth factors[72] along with analgesic effects [73,74] and suppressing bacterial proliferation.[75]

Seyed Hamid Salehi et al conducted a prospective randomized clinical trial between February 2009 and October 2009 in Motahari Burn Hospital, Tehran. The aim of the study was to compare Amniotic membrane with Vaseline gauze for donor site dressing of split-thickness skin graft in patients undergoing burn wound reconstructive surgery.

The intervention site dressing was done with amniotic membrane, whereas Vaseline impregnated gauze was used to dress the control site. After isolating amniotic membrane from the placenta, it was

washed several times with normal saline and sodium hypochlorite 0.05%. It was dried and sterilized with gamma waves (25 kGy).

Their results showed greater pain score and delayed healing in the control group than the intervention group. They concluded that amniotic membrane can be used as an alternative dressing for skin graft donor sites as it increases patients' comfort by reduction in pain sensation and improvement of overall the process of wound healing.[76]

In 2015, a study was published by Serag M. Zidan et al which aimed to determine the clinical efficacy of HAM that was preserved in 98% glycerol for its application as biological dressing to manage the donor site of split thickness skin graft (STSG). Its effect was compared with chlorhexidine impregnated vaseline gauzes. They used parameters such as rapidity of healing, associated pain and infection. The study enrolled forty subjects and was conducted in Al-Azhar University Hospitals from August 2013 to June 2014. In the HAM group, HAM was used as a primary donor site dressing. In the control group, chlorhexidine-impregnated paraffin gauze was applied as the primary dressing over donor site. They observed that HAM group showed significantly lower pain, shorter time to reepitheialization with no difference in infection rate.[77]

The most appealing feature promoting use of HAM as a biological dressing is its abundance, low cost and ease of harvesting.[78] Multiple methods to preserve HAM have are there such as cryopreservation, use of Glycerol, freeze drying and gamma irradiation. These methods assume significance as HAM has short shelf life.[79] The risk of disease transmission is a possible drawback of using human-derived biological dressings.

Another method described for pain relief at donor site is altering the site of graft harvest altogether. Akan et al conducted a study and published in 2003 with sole aim directed at importance of donor site pain. Their technique was described to eliminate donor-site pain and they harvested the skin graft from the flap which after elevation is insensate. In 15 patients, they used donor site as overlying skin of the flap that had been used for reconstructive purposes (group I). In other

23 patients, the donor site was posterolateral thigh (group II). It was found that group I had significantly lower mean pain scores than group II. They concluded that when consideration is of donor-site pain, this procedure avoids postoperative donor site pain and leads to an uneventful and comfortable healing.[15]

Fractional autologous full thickness skin grafting (FFTSG) is another procedure described to minimize donor site pain. The harvest of multiple, discontinuous, narrow skin columns (i.e. microcolumns), which represent a portion of a predetermined skin surface area, is done. The fractional micrometric wounds heal by remodeling and have full reconstruction of normal tissue architecture with complete functionality. Jaller et al published their study in 2018 in which they evaluated the pain at donor site with this procedure. They evidenced that the harvest of FTSGs was associated with minimal pain.[80]

Simple measures such as ice application for donor site pain relief have also been studied. Ice application has been in vogue since many years as a local anesthetic, and has the ability to ease pain. This analgesic effect is believed to be due to the affect of cold in reduction of nerve conduction velocity.[81,82]

This property of ice was utilized by Akan et al. They did a study in 2001-2002 and applied ice to minimize the pain at the donor site of split thickness skin graft. Thirty-six patients were included in this study. It was demonstrated that patients in whom ice was used had a significant reduction in donor site pain.[83]

Apart from a variety of dressing materials being discussed and reviewed for donor site pain relief, local applications of numerous agents have been tried with variable results for achieving this goal. A variety of agents such as Morphine and Local anaesthetic agents like lignocaine, bupivacaine, ropivacaine have been tried in various modalities for administration.

Many studies have been done to evaluate topical opioid application for pain relief at the donor site. Opioids are very useful in treating moderate to severe pain. Systemic administration can have many

adverse effects. In clinical practice, the topical application of opioids has been done for corneal wounds, oral mucosa and the skin.

A randomized controlled study was done by Zaslansky et al in 2013 for assessment of analgesic potential of topically administered morphine over STSG donor sites. In the study, which included forty-four patients, varying doses of morphine in hydroxyethylcellulose gel or a placebo were applied on the excised split-thickness donor sites. They found no difference in pain scores or use of supplementary analgesic requirements between the groups. So, they came to a conclusion that topically applied morphine gel onto standardized skin wounds did not provide pain relief.[84]

Another study by Fransen et al in 2016 also concluded that the morphine gel showed no advantage over a placebo in relieving donor site pain.[85]

A study by Goodacre et al in late 80's was conducted to evaluate analgesic efficacy of EMLA cream in comparison with infiltration of lignocaine 0.5 % solution while harvesting the skin grafts. EMLA cream is formulated as eutectic mixture of local anesthetic drug, lignocaine and prilocaine, in emulsifying agent, stabilizing agent and water. They observed that in process of graft harvest, the anaesthetic effect produced by EMLA was equally effective to that produced via infiltration of lignocaine. But, infiltration caused variable degrees of pain. Instead no discomfort was observed with EMLA application. So they said that EMLA can be the first choice if skin graft harvesting has to be done under local anaesthesia.[86]

Owen et al reported in their study that 2% lignocaine gel when applied to a skin graft donor site provided a statistically significant reduction of pain over the first week and there was no affect on wound healing.[87]

Lignocaine toxicity is manifested by cardiac arrythmias and hypotension. The concerns in this regard had led to stoppage of lignocaine gel application at many centres. A study done by Bulmer and Duckett in 1985 had conclusively proven that when lignocaine gel is applied topically, systemic absorption is minimal and doesn't reach toxic concentrationsin plasma.[88] Read et al also showed in their study

that plasma levels of lignocaine were consistently low in majority of the patients receiving topical application.[89]

Desai et al in their study in 2013 compared the effectivity of two different preparations, emulsion and aqueous, of local anaesthetic agent lidocaine in providing analgesia over donor sites while changing the dressing. They concluded that the topically applied local anaesthetic preparations resulted in less pain scores while changing the dressing. Also, the mean plasma concentrations were well within the safety profile of the anaesthetic agent.[90]

In a study published in 1999 by Jellish et al, the topical local anaesthetic agents 2% lidocaine, 0.5 % bupivacaine were compared with Normal Saline as control. The study aimed to determine if these topical agents could reduce the associated pain and subsequent analgesic requirements on application at skin harvest sites. They reported increase in heart rates with the saline group. It was also observed that pain scores were lower and less narcotic requirement was there in patients receiving lidocaine. However, the plasma levels of lidocaine were found higher than 0.5 % bupivacaine. But, none of the agents had reached their toxic levels.[91]

A study was done by Nandhagopal et al and published in 2015 to evaluate the role of topical lignocaine solution for acute pain relief in 1st and 2nd degree burns patient. They found no difference in pain relief and no decrease in total analgesic consumption in study group receiving topical application of 2% lignocaine to that of the control group receiving normal saline topically. They concluded that this result is likely due to a shorter duration of action of lidocaine and advocated trials of longer acting agents such as bupivacaine for topical application.[92]

A study done in 1989 by Chester et al consisted of thirty patients undergoing cholecystectomy. The patients received 0.5% bupivacaine for wound perfusion for first 24 hours and this was followed by Normal saline perfusion for next 24 hrs or the other way round i.e receiving normal saline first and 0.5% bupivacaine in later 24 hrs. The analgesia was administered by use of a patient controlled analgesic device which

delivered Pethidine bolus on demand for pain relief. Chester et al noticed that patients in both the groups required higher analgesics on the first postoperative day. But, they also observed a lower pain score with bupivacaine, along with less number of bolus dosages on the day bupivacaine was used for wound perfusion. So, they concluded that surgical wounds on bupivacaine perfusion have better pain relief than saline.[93]

Kadar et al assessed the pain relieving effect of bupivacaine 0.5% applied locally in tonsillar fossa after tonsillectomy. After tonsillectomy, packing of the right tonsillar fossae was done with tonsillar gauze that was soaked in 0.5 % bupivacaine solution for 5 minutes. Packing in the left fossae as control was done with swab soaked in 0.9 % normal saline. They concluded that that bupivacaine with topical application of in the tonsillar fossa, a reduction in post operative pain over the site can be achieved.[94]

Zohar et al. from Tel Aviv University studied the role of bupivacaine for pain relief in 36 patients after total abdominal hysterectomy and bilateral salpingooophorectomy. They divided patients in two groups. In one group (G1), they instilled 0.25% bupivacaine solution and in second group (G2), they instilled sterile water. When compared G1 required significantly less rescue analgesia ($p < 0.001$) than G2.[95]

In a study by Goldstein et al from Paris, the role of local anesthetics in preventing postoperative pain after laparoscopic gynecologic surgery was studied. In each patient, the operating surgeon instilled 20 ml of either0.5% bupivacaine solution, 0.75% ropivacaine solution or normal saline depending upon the group. It was found that analgesia (morphine) requirement was considerably less in bupivacaine group than normal saline group ($p < 0.05$).[96]

After harvesting bone graft from anterior iliac crest, many patients reportedly feel severe pain at the donor site. In their study in 2006-2007, Barkhuysen et al divided the patients after anterior iliac crest bone harvest into two groups. While one group received single dose of bupivacaine, the other group did not. They aimed to study the effect of single dose of bupivacaine for the pain relief at site of harvest. They

observed no difference in the post operative pain between the bupivacaine and the control group.[97]

The study done by Hernandez et al in 2011-2012 administered local anesthetic agent bupivacaine as a continuous infusion to manage the pain at STSG donor site. After harvesting the graft, subcutaneous catheter placement over donor site was done to infuse the local anaesthetic agent. In donor sites which were less than 4 inches in width, placement of single catheter was done. For the sites greater that 4 inches in width, a dual catheter system was used. An elastomeric pump enabled continuous delivery of 0.5% bupivacaine at rate of 4 ml/hr. The average duration of anesthetic infusion was 3.1 days. They noted a substantial reduction in worst, least, and average donor site pain scores from the first post operative day to the second postoperative day and observed this similar effect through postoperative day 3.[98]

Similarly, Gamli et al in 2012 did a study and found that the patients in whom the bupivacaine soaked gelfoam was placed at iliac crest harvest site, a decrease in post operative analgesia usage was found. But there was no significant difference observed in visual analogue scale scores for pain.[99]

R. Alvi et al did a study for assessing safety of depot preparations of bupivacaine and ketoprofen on application over donor site of STSG. The study included two groups of six patients who received either bupivacaine gel (2.5 mg/ml) or ketoprofen gel (1.6 mg/ml). . Assessment of the serum levels was done using Gas Liquid Chromatography and High Pressure Liquid Chromatography. Mean levels of bupivacaine obtained was 0.07 pg/ml (range 0.03-0.1).Toxic serum level for bupivacaine has been reported to be 4ug/ml. They concluded that possibility of such preparations on application at denuded dermis resulting in toxic levels is quite unlikely.[100]

Fischer et al conducted a study in 2003 to determine the safety of bupivacaine infiltration subcutaneously over donor site for STSG harvest. The study consisted of fourteen patients. The average age in study was 14.3 years. The administered dose of bupivacaine was

significantly lower than 3mg/kg. They observed that highest levels of bupivacaine obtained were well below the safe upper limit in children. Also, no signs of toxicity were noted.[18]

There was a prospective randomized double-blind trial done by Morris et al in 1990. They compared the effects of dressings on donor site pain and healing. The study involved use of Opsite alone, Opsite after application of bupivacaine, scarlet ointment dressing alone and scarlet ointment after bupivacaine. They noted that pain was significantly lesser with Opsite dressing. This effect was considered due to the non mobile nature of opsite. Also, many patients with scarlet ointment dressing felt no pain. It was concluded that the major role in pain is the movement of dressings. Bupivacaine appeared to have no effect.[101]

However, in a study by Butler et al in 1993 evaluation of the effect of dressing treated in different ways on post operative STSG donor site pain relief was done. The dry calcium alginate dressing, Kaltostat dressing moistened with saline and a Kaltostat dressing moistened with bupivacaine hydrochloride (0.5 %) were compared. They noticed a significant decrease in donor site pain in Kaltostat moistened with 0.5% bupivacaine group than the other two groups. They, thus, showed that addition of Bupivacaine to Kaltostat provided pain reduction on donor site and there also was no evidence of reduction of beneficial effects of kaltostat on donor site healing.[102]

In another study performed in Nigeria, Oluwatosin and his colleagues used 0.5% aqueous solution of bupivacaine hydrochloride for application to donor site of split thickness skin graft. They found out in their study that the patients treated with bupivacaine solution on donor site had reported a significant less pain reduction on the donor site on comparison to those in whom donor site was not treated with any solution.[103]

In a prospective study in 2000-2001 in Thailand by Jenwitheesuk et al, forty patients were included who required STSG for defect reconstruction. The patients were randomly divided into two groups. In Group A, dressings moistened with bupivacaine 0.5% in dose of 6 ml per 100 cm^2 of donor site area was used. The solution was instilled via

catheter every 12 hours under aseptic technique. The control group, Group B, received dressings moistened with saline and 6 ml of saline for 100 cm^2 of donor site area was administered in similar fashion and interval as the study group A. They found in their study that dressing soaked with bupivacaine 0.5% provided a significant pain relief on the donor site in the early post operative with p values<0.001.[104]

A more recent study conducted by Muhammad Raza et al included one hundred and fifty patients requiring split thickness skin grafting for various soft tissue defects. The patients were divided in two groups, A and B, and each group comprised of 75 patients. In Group A, dressing at skin graft donor site was kept moist with 0.25% bupivacaine solution. For every 100 cm^2 of the donor site area calculated, 12 ml of 0.25 % bupivacaine was administered. For the control Group B, same amount of saline was used to keep the donor site dressing moist. The calculated amounts of saline and 0.25 % bupivacaine were instilled through catheter placed over donor site once immediately after the surgery and same amount was repeated after 12 hours. Requirement of the rescue analgesia in 24 hours was used to measure the outcome. Effectiveness of bupivacaine soaked dressing was 93.3% in comparison to conventional dressing with only 4% effectiveness. They concluded that dressing soaked with 0.25 % Bupivacaine proved to be more effective in pain relief and also in reduction of the amount of rescue analgesics required on comparison with conventional saline moistened dressing.[105]

Liposomal preparations of bupivacaine have also been used for pain relief at donor site. Dissanaike et al in 2018 reported that infiltration of liposomal bupivacaine preparation into the graft donor sites in burns patients undergoing skin grafting resulted in effective pain relief at the donor site.[106]

Another local anaesthetic agent Ropivacaine has been used for donor site pain relief. In the study by Trost et al, Ropivacaine infiltration over donor site resulted in relief of pain at donor site.[107]

Thus, after analyzing the abundance of literature including dressing materials and modalities, there was no conclusive evidence with regard

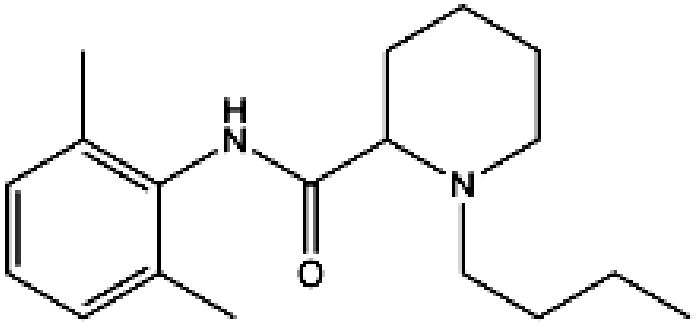
to donor site pain relief. Although role of local anaesthetic agents is described, the results obtained have been contrary and studies have used a higher concentration of the agent Bupivacaine. We decided to conduct this prospective study to compare the efficacy of 0.125 % Bupivacaine moistened dressing, an even lesser concentration, with conventional saline dressings for donor site pain relief.

PHARMACOLOGY

BUPIVACAINE:

Bupivacaine belongs to amide group of local anaesthetics. It is four times as potent as lidocaine and has pKa of 8.1.[108]

Chemical Structure



Chemical Name

1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamide

Molecular Formula

$C_{18}H_{28}N_2O$

Mechanism of Action

It prevents transmission of nerve impulses (conduction blockade) by inhibiting passage of sodium ions through ion selective sodium channels in nerve membranes.

Pharmacokinetics

Systemic absorption of local anesthetics is determined by the site of injection, the dosage & volume, the addition of vasoconstrictor agent and the pharmacological profile of agent itself.[109]

It has long plasma half life (2.7 hrs.) accompanied by low plasma clearance (0.47 L/min.). It is about 95% protein bound, mainly to α1 Acid Glycoprotein. Most of the drug is metabolized in the liver & about 5% appears unchanged in the urine.[109]

Bupivacaine crosses the placenta, however it is approved for use in obstetric anaesthesia.

Indications

It can be used for any nerve blocks except Intravenous Regional Anaesthesia (IVRA).

Can be given in:

- Spinal anaesthesia
- Epidural anaesthesia – As single injection or continuous epidural

Infusion

- Peripheral nerve blocks
- Infiltration anaesthesia

Dosage & Administration: Maximum safe dose – 2mg/kg

TOXICITY: It is related to plasma level of unbound drug and most likely seen after inadvertent intravenous injection. Bupivacaine exerts direct action on both heart & blood vessels. Around 1980, clinical reports indicated that bupivacaine possessed a relatively high potency for cardiotoxicity.[110] It was also found that patients with cardiac depression or arrest due to bupivacaine toxicity could be unexpectedly difficult to resuscitate, especially if the patient was in late pregnancy.[111]

MATERIALS AND METHODS

Source of Data

All patients admitted to Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital, Ludhiana who required split thickness skin grafting for various indications and who were willing to be a part of the study, were included in the study.

INCLUSION CRITERIA

- All patients requiring split thickness skin grafting and were willing to participate in study
- Donor site – thigh
- Age 10-60 years

EXCLUSION CRITERIA

- History of allergy to any local anaesthetic
- Any cardiac history

This randomized, prospective, comparative study was conducted at Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital, Ludhiana over a two year period. The patients were randomly divided into two groups with 30 cases in each group. Random number table was used for this purpose. Group A included patients with 0.125% bupivacaine moistened dressings. Group B comprised of patients in which conventional dressings were used.

In both the groups, split thickness skin graft was harvested using standard aseptic procedure. Once the desired amount of the graft was harvested and complete hemostasis was confirmed, the donor site wound was assessed for its dimensions. Donor site wound was covered with Vaseline gauze, then covered by a thin layer of sterilized gauze, a catheter was longitudinally placed on this layer of gauze on the wound which in turn was covered with abundant sterile gauzes and finally crepe bandage was applied to prevent any external contamination.

In Group A, the donor site dressing was kept soaked by instilling an aqueous solution of 0.125 % bupivacaine hydrochloride through the catheter under all aseptic techniques. The amount instilled depended

upon the size of the graft taken. For every 100 cm^2 of the donor site wound, 12 ml of bupivacaine solution was instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

In Group B, the donor site dressing was moistened by instilling normal saline through the catheter under all aseptic conditions. Just like Group A, in Group B for every 100 cm^2 of the donor site wound 12 ml of the normal saline was instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

For the assessment of pain, patients were interviewed for pain using Visual Analogue Scale(VAS) every 8 hours by an independent observer. Patients with complains of pain or in whom pain score was more than 4 (i.e. need for analgesia), were given intravenous (IV) analgesia in the form of tramadol(50mg).

Final conclusion of analgesia sparing effect of the dressings was made at 24 hours postoperatively and any side effects were also noted.

DURATION OF STUDY/ NUMBER OF CASES: 30 in each group

OUTCOME: Pain assessment using VAS

STATISTICAL ANALYSIS

Data were described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student t-test. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency was less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

OBSERVATION AND RESULTS

This randomized, prospective, comparative study was conducted at Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital, Ludhiana over a two year period. The patients were randomly divided into two groups with 30 cases in each group. Random number table was used for this purpose. Group A (Bupivacaine group) included patients with 0.125% bupivacaine moistened dressings. Group B (NS group) comprised of patients in which conventional saline dressing was used.

The results of the study are as follows:

PATIENT DEMOGRAPHICS:

TABLE 1: GENDER DISTRIBUTION IN STUDY

GENDER	No. of cases	Percentage
Female	14	23.3%
Male	46	76.7%
Total	60	100.0%

The present study comprised of 60 cases in total with 30 cases in each group. The total number of males in the study were 46 comprising 76.7%. A total of 14 females formed a part of the study.

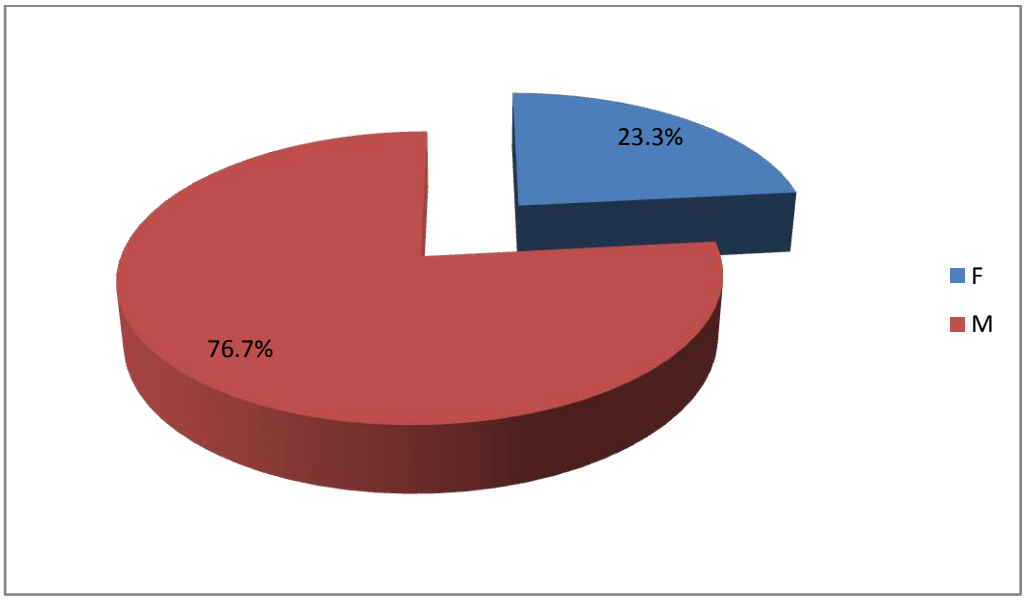


FIGURE 1: GENDER DISTRIBUTION IN STUDY

TABLE 1a: SIGNIFICANT PAST HISTORY

PAST HISTORY	No. of cases	Percentage
NOT SIGNIFICANT	60	100.0%

There was no significant past history in both the study groups.

TABLE 1b: ALLERGY TO LOCAL ANAESTHETICS

H/O ALLERGY TO LOCAL ANAESTHETICS	No. of cases	Percentage
NIL	60	100.0%

None of the patients forming the study group had any history of allergy to a local anaesthetic agent. A history of allergy to the local anaesthetic agent was part of our exclusion criteria.

TABLE 2: GENDER DISTRIBUTION IN BOTH GROUPS

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		Bupivacaine		NS				
SEX	F	5	16.7%	9	30.0%	14	1.491	0.222
	M	25	83.3%	21	70.0%	46		
Total		30	100.0%	30	100.0%	60		

In the bupivacaine group, out of total of 30 cases, 5 were females comprising 16.7% population. 25 male patients were there in bupivacaine group.

In the NS group, a total of 9 females and 21 males formed part of the group.

This difference in gender distribution was not statistically significant with p value =0.222. Thus, both the groups were demographically similar in gender distribution.

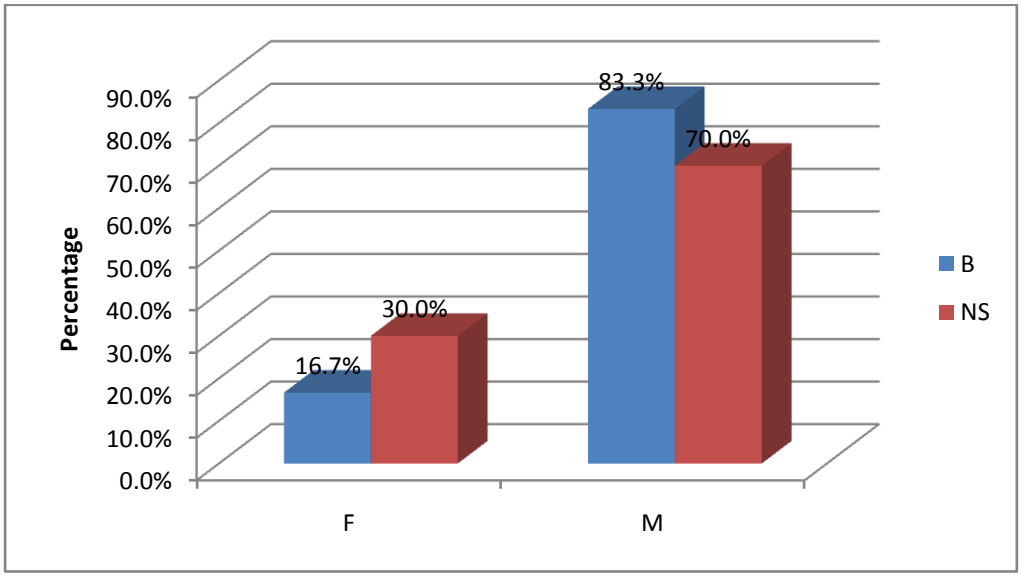


FIGURE 2: GENDER DISTRIBUTION IN BOTH GROUPS

TABLE 3: AGE DISTRIBUTION

	B		NS		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
AGE	34.83	14.26	33.40	14.55	0.385	0.701	-6.01	8.88

The mean age in the bupivacaine group was 34.83 years with a standard deviation of 14.26. The NS group had mean age of 33.40 years with a standard deviation of 14.55. The two groups were comparable in terms of age with no statistical significance.

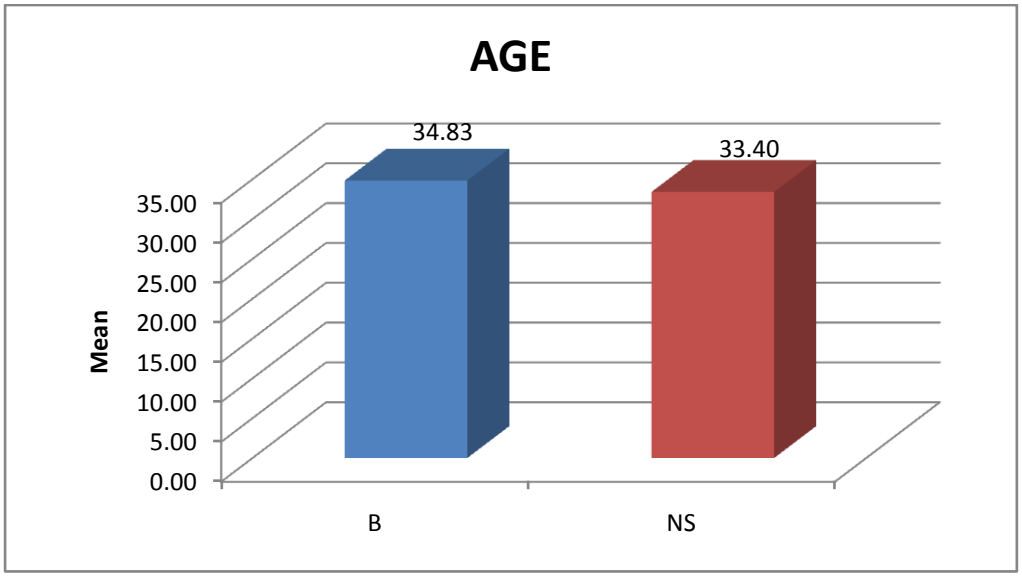


FIGURE 3: AGE DISTRIBUTION

Table 4: ASSOCIATED ILLNESS IN THE PATIENTS

ASSOCIATED ILLNESS	No. of cases	Percentage
NIL	39	65%
AML	1	1.7%
ASTHMA	1	1.7%
DM	2	3.3%
DM,HCV	1	1.7%
DM,HTN	1	1.7%
DRUG ADDICT	1	1.7%
EYEBROW LACERATION	1	1.7%
GRADE 2 SACRAL SORE	1	1.7%
H/O FACIAL PALSY	1	1.7%
HEMORRAGIC CONTUSIONS	1	1.7%
HYPERTENSION	1	1.7%
HYDROPNEUMOTHORAX	1	1.7%
L1 FRACTURE PLATING	1	1.7%
L2, RIGHT TIBIA FRACTURE	1	1.7%
LEFT BELOW ELBOW AMPUATAION	1	1.7%
LEFT LATERAL MALLEOLUS FRACTURE	1	1.7%
LEFT PELVIC FRACTURE	1	1.7%
OPEN FRACTURE TIBIA LEFT	1	1.7%
SEIZURE DISORDER	1	1.7%
ULNA FRACTURE LEFT, RADIAL A,ULNAR,MEDIAN N	1	1.7%
Total	60	100.0%

No associated illness was present in majority of the study population. Diabetes Mellitus was the commonest associated co morbidity. It was seen in 4 patients. Isolated Diabetes in 2 patients and associated with Hypertension and Hepatitis C reactivity in 1 patient each was seen.

TABLE 5: MODE OF INJURY

MODE OF ONSET	No. of cases	Percentage
ASSAULT	1	1.7%
BURN(ACID)	1	1.7%
BURN(SCALD)	1	1.7%
BURNS(ELECTRIC)	16	26.7%
BURNS(FLAME)	10	16.7%
BURNS(THERMAL)	1	1.7%
DOG BITE	1	1.7%
MACHINE INJURY	2	3.3%
RSA	18	30.0%
SPONTANEOUS	4	6.7%
TRAUMA	5	8.3%
Total	60	100.0%

The commonest mode of injury for which patients required STSG was burns followed by road side accidents.

Among the burns, electrical burns were the commonest, followed by flame burns.

TABLE 5a: MODE OF ONSET OF INJURY

MODE OF ONSET	No. of cases	Percentage
BURN	29	48.3%
RSA	18	30.0%
TRAUMA	5	8.3%
SPONT	4	6.7%
MACHINE INJURY	2	3.3%
ASSAULT	1	1.7%
DOG BITE	1	1.7%
Total	60	100.0%

TABLE 5c: COMPARING MODE OF ONSET IN BOTH GROUPS

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
MODE OF ONSET	BURN	15	50.0%	14	46.7%	29	7.723	0.259
	RSA	7	23.3%	11	36.7%	18		
	TRAUMA	4	13.3%	1	3.3%	5		
	SPONT	1	3.3%	3	10.0%	4		
	MACHINE INJURY	2	6.7%	0	0.0%	2		
	ASSAULT	0	0.0%	1	3.3%	1		
	DOG BITE	1	3.3%	0	0.0%	1		
Total		30	100.0%	30	100.0%	60		

In both the groups the commonest mode of onset was burn injuries, followed by road side accidents.

Thus, both the groups were similar in the mode of onset of injuries and so the indications for the STSG.

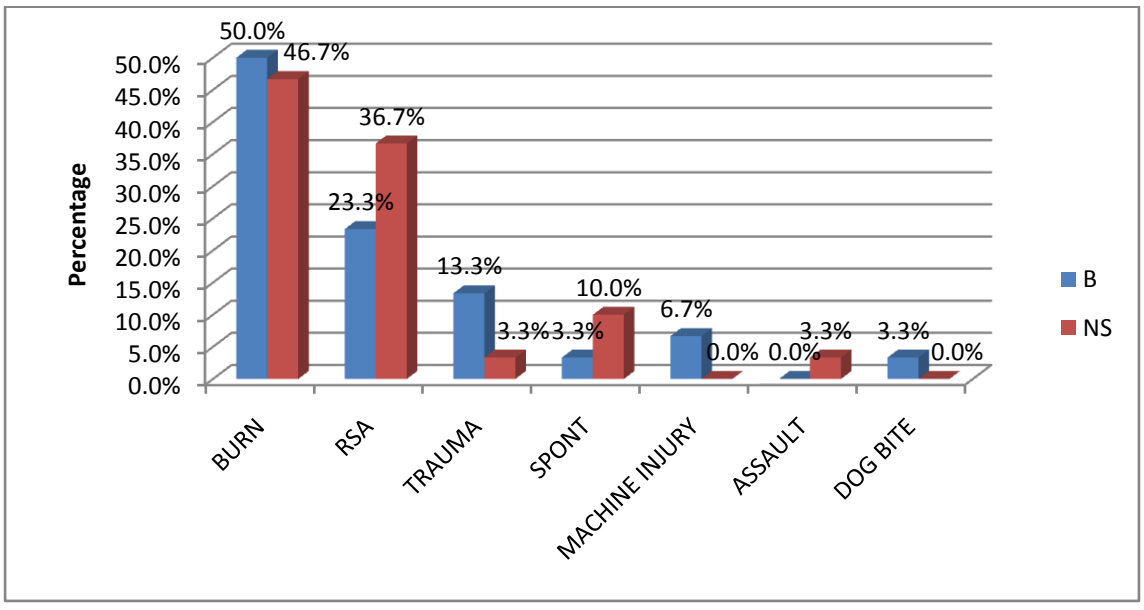


FIGURE 4: COMPARING MODE OF ONSET IN BOTH GROUPS

TABLE 6: TYPE OF ANAESTHESIA ADMINISTERED

TYPE OF ANAESTHESIA	No. of cases	Percentage
GA	45	75.0%
LA	1	1.7%
SA	14	23.3%
Total	60	100.0%

In 45 cases out of 60, general anaesthesia was administered for the procedure . 14 cases were performed under spinal anaesthesia. In one patient, the graft was harvested by local anaesthetic, lignocaine, infiltration at the donor site.

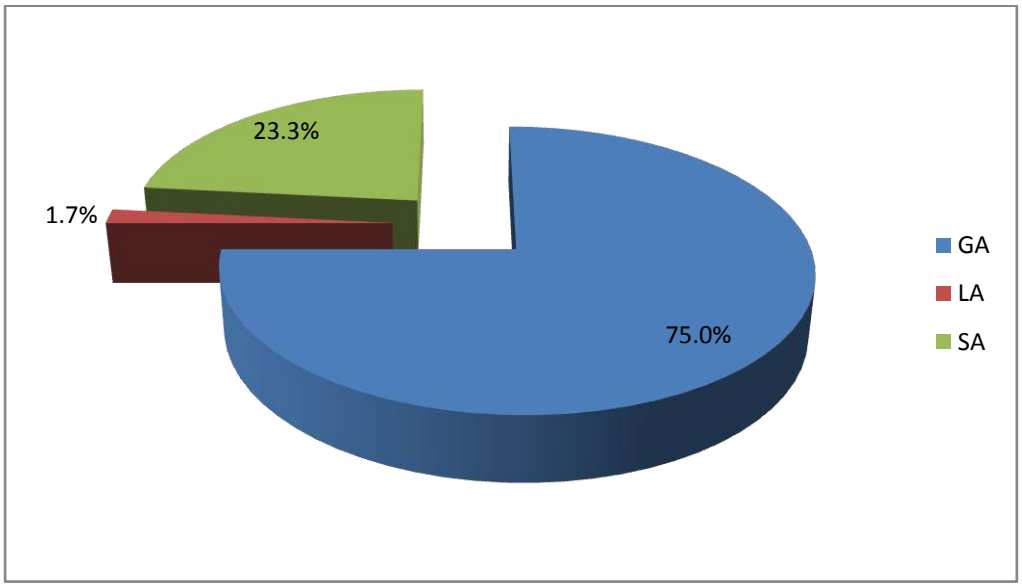


FIGURE 5: TYPE OF ANAESTHESIA ADMINISTERED IN STUDY

TABLE 7: COMPARING TYPE OF ANAESTHESIA IN BOTH GROUPS

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
TYPE OF ANAESTHESIA	GA	23	76.7%	22	73.3%	45	1.308	0.520
	LA	1	3.3%	0	0.0%	1		
	SA	6	20.0%	8	26.7%	14		
Total		30	100.0%	30	100.0%	60		

In Bupivacaine group, 23 patients received general anaesthesia for the procedure and 6 patients received spinal anaesthesia. The saline group comprised of 22 patients in whom general anesthesia was administered. 8 patients in the saline group received spinal anaesthesia. Thus, the two groups were similar in respect to the type of anaesthesia used for the procedure with p =0.520

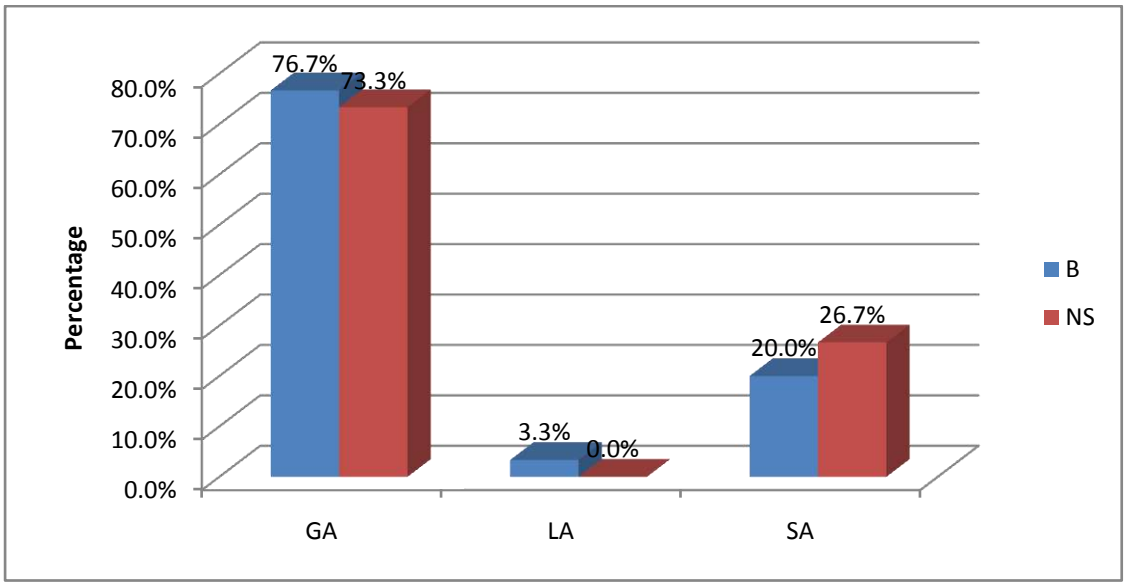


FIGURE 6: COMPARISON OF TYPE OF ANAESTHESIA IN BOTH GROUPS

TABLE 8: DONOR SITE COMPARISON

DONOR SITE(THIGH)	No. of cases	Percentage
LEFT	31	51.7%
RIGHT	29	48.3%
Total	60	100.0%

In both the groups, thigh was the donor site for harvesting the split thickness thin graft. In 31 cases, left thigh was used as the donor site while in 29 cases right thigh was selected as the donor site.

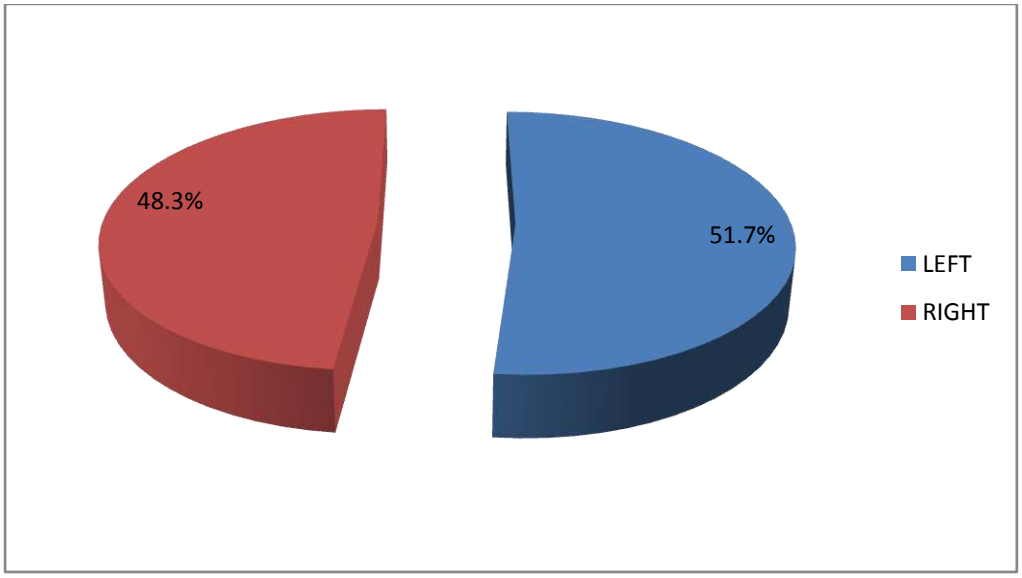


FIGURE 7: DONOR SITE COMPARISON

TABLE 9: COMPARING DONOR SITES IN BOTH GROUPS

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
DONOR SITE (THIGH)	LEFT	18	60.0%	13	43.3%	31	1.669	0.196
	RIGHT	12	40.0%	17	56.7%	29		
Total		30	100.0%	30	100.0%	60		

Both the groups showed no statistical difference whether right or left thigh was selected as donor site for graft harvest.

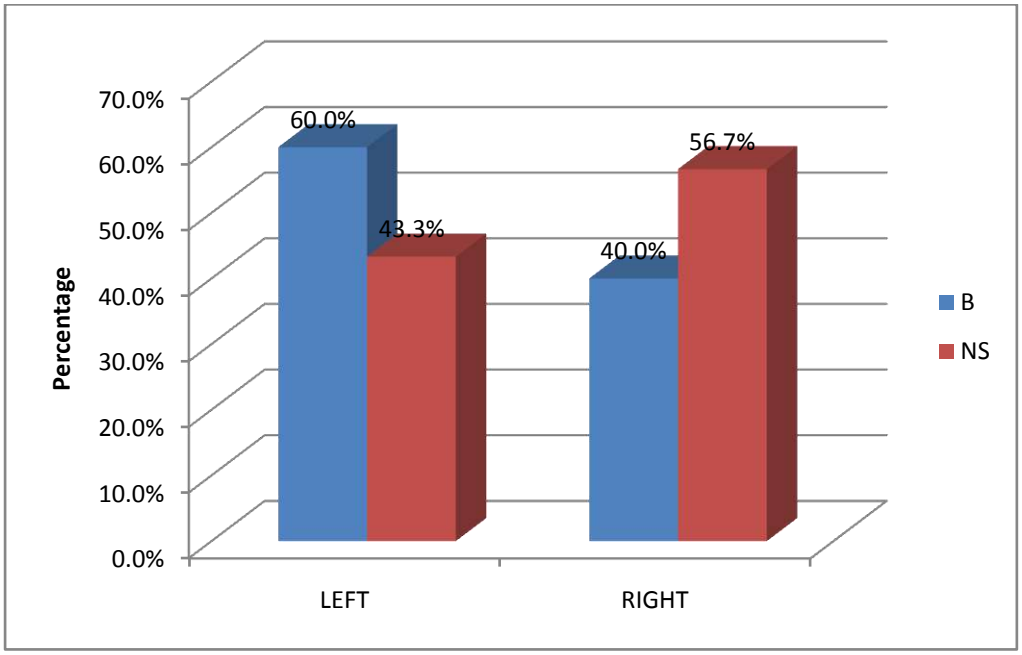


FIGURE 8: COMPARING DONOR SITE SIDES IN BOTH GROUPS

TABLE 10: DURATION OF INJURY AND DONOR SITE AREA

	B		NS		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
DURATION (DAYS)	194.77	581.92	45.30	94.19	1.389	0.170	-65.97	364.90
DONOR SITE AREA (CM2)	289.20	176.09	352.27	258.84	-1.103	0.274	-177.48	51.34

The mean days taken for the procedure were 194.77 days in bupivacaine group. In the saline group, a smaller duration was observed. But this difference held no statistical significance.

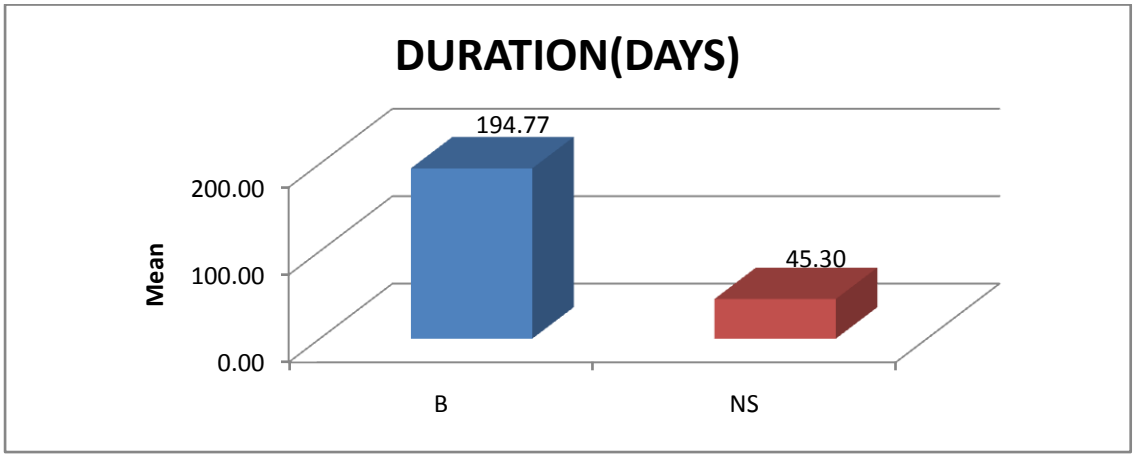


FIGURE 9: DURATION OF INJURY

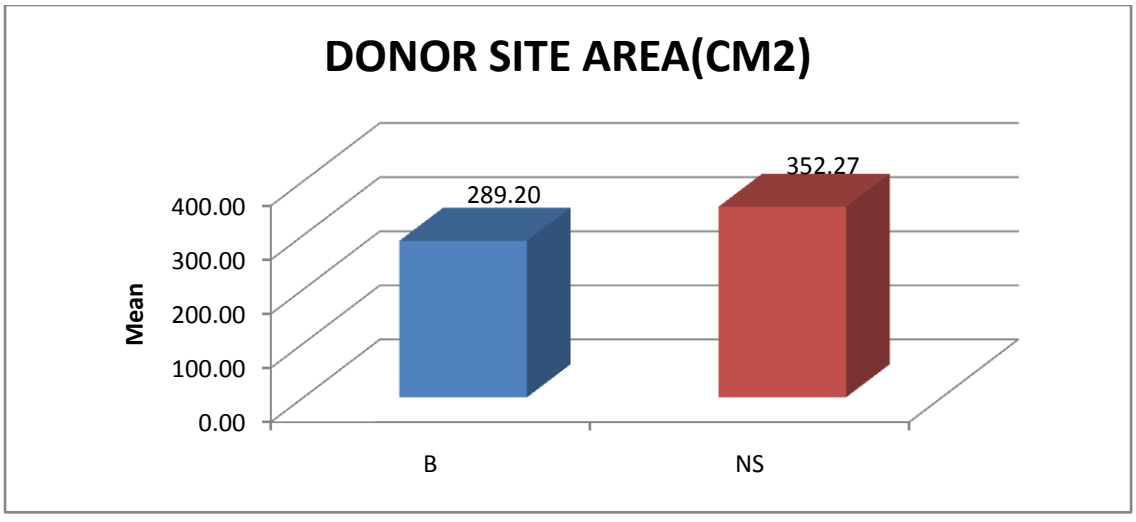


FIGURE 10: MEAN DONOR SITE AREA IN BOTH GROUPS

The donor site area showed a mean of 289.20 cm^2 in the bupivacaine group. For the saline group, mean of the donor area was 352.27 cm^2. Both the groups were similar in terms of the area of the donor site.

TABLE 11: QUANTITY OF BUPIAVACAINE AND SALINE ADMINISTERED

	B		NS		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
QUANTITY (ML)	34.70	21.13	42.24	31.04	-1.100	0.276	-21.27	6.18

The quantity of bupivacaine used for moistening the donor area had a mean of 34.70 ml. In saline group, the quantity used had a mean of 42.24 ml. However, this difference observed was statistically not significant with p value=0.276

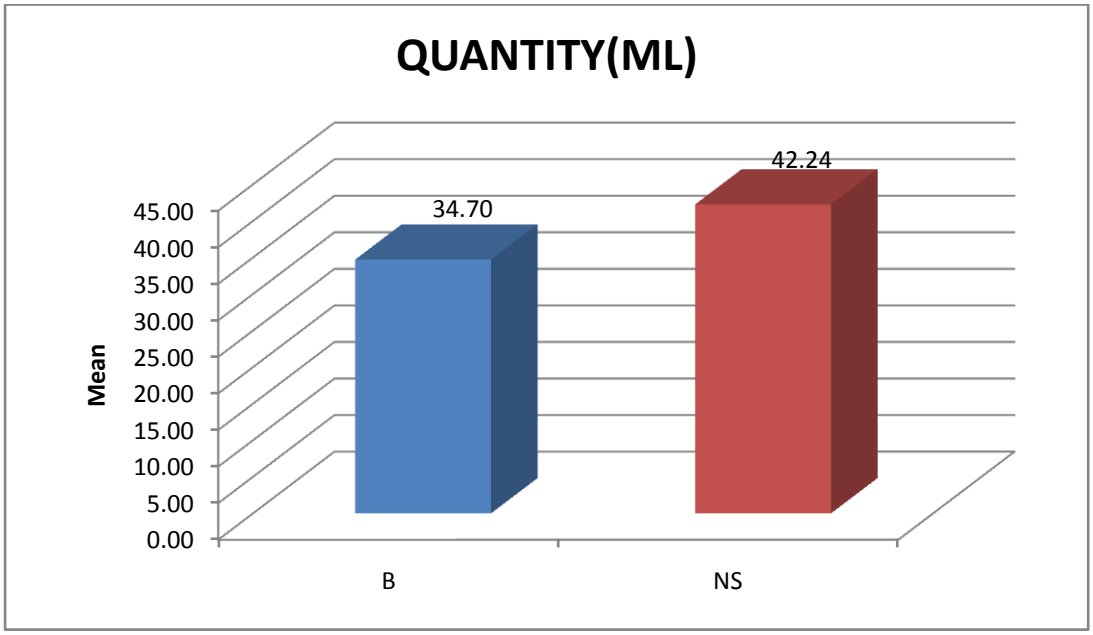


FIGURE 11: QUANTITY OF BUPIAVACAINE AND SALINE ADMINISTERED

TABLE 12: DONOR SITE PAIN AT 8 HOURS AND RESCUE ANALGESIA

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
Donor Site Pain at 8 hrs	No	27	90.0%	13	43.3%	40	14.700	0.000
	Yes	3	10.0%	17	56.7%	20		
Total		30	100.0%	30	100.0%	60		

At 8 hours post instillation, in the bupivacaine group, 27 patients reported no pain at donor site while 3 patients had pain at donor site(pain score >4). The saline group comprised of 17 patients who reported the donor site to be painful (pain score > 4). This difference was statistically significant with a p value = 0.000.

Thus, rescue analgesia in form of tramadol was administered to only 3 patients in the bupivacaine group compared to 17 patients in saline group at 8 hours and showing a statistically significant difference in number of patients reporting pain and subsequently requiring rescue analgesia in both the groups.

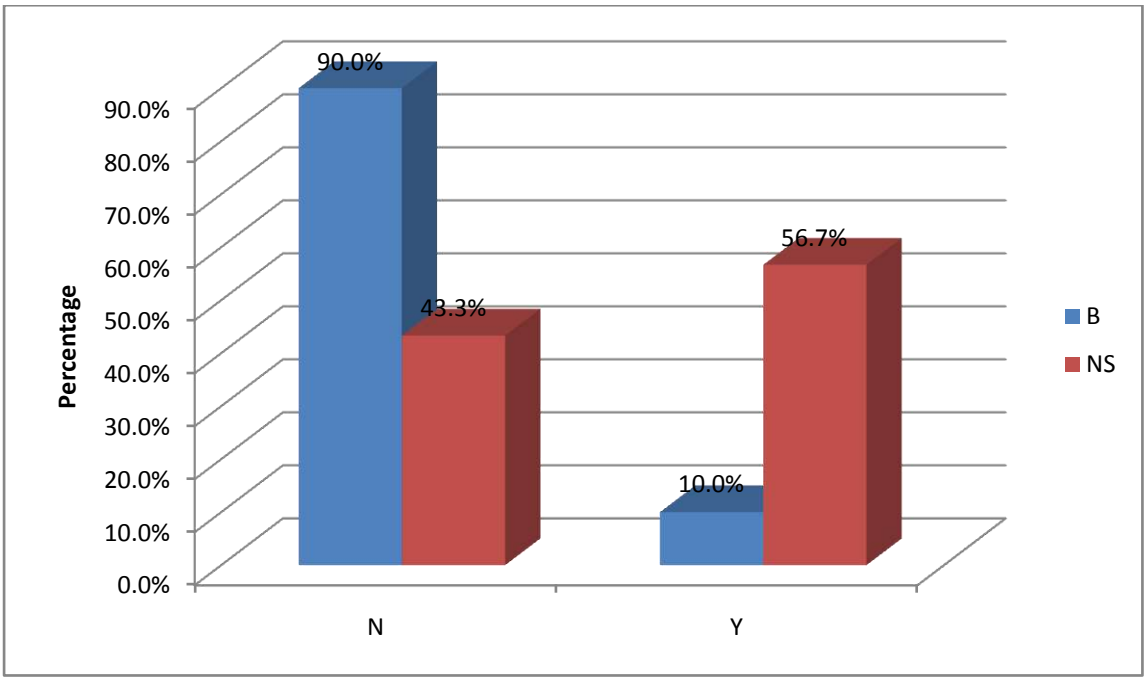


FIGURE 12: DONOR SITE PAIN AT 8 HOURS AND RESCUE ANALGESIA

TABLE 13: DONOR SITE PAIN AT 16 HOURS AND RESCUE ANALGESIA

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
Donor Site Pain At 16 hrs	No	29	96.7%	8	26.7%	37	31.093	0.000
	Yes	1	3.3%	22	73.3%	23		
Total		30	100.0%	30	100.0%	60		

The assessment at 16 hours revealed the donor site to be painful (pain score >4) in 1 patient among 30 in the bupivacaine group. In the saline group, the donor site pain was reported by 22 patients. Thus, no donor site pain was there in 96.7 % of patients in bupivacaine group compared to 26.7 % in saline group. This difference holds statistical significance.

Thus, at 16 hours, in bupivacaine group rescue analgesia was administered to 1 patient compared to 22 patients in the saline group.

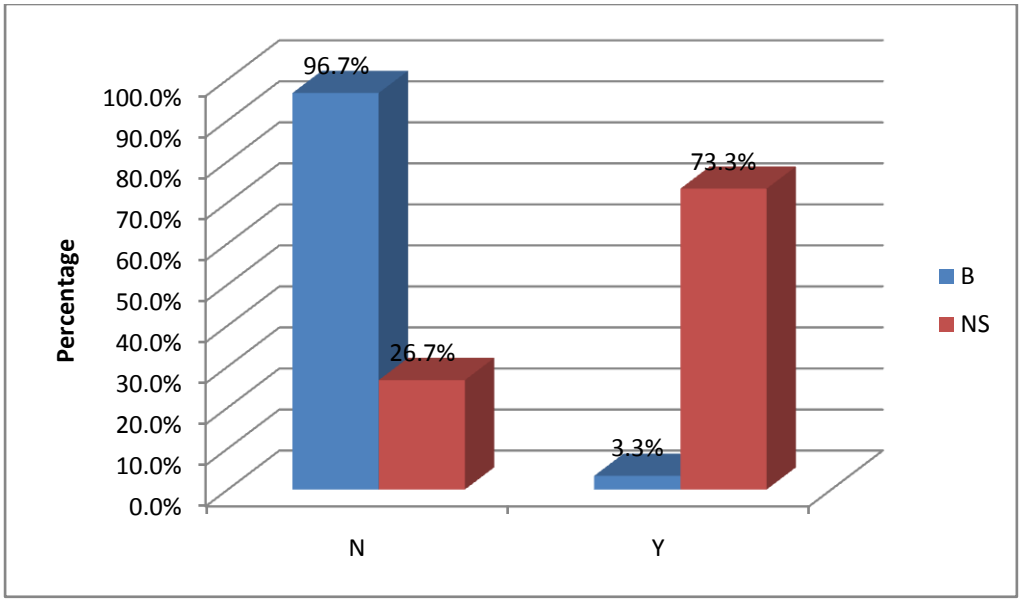


FIGURE 13: DONOR SITE PAIN AT 16 HOURS AND RESCUE ANALGESIA

TABLE 14: DONOR SITE PAIN AT 24 HOURS AND RESCUE ANALGESIA

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
Donor Site Pain At 24 hrs	No	28	93.3%	21	70.0%	49	5.455	0.020
	Yes	2	6.7%	9	30.0%	11		
Total		30	100.0%	30	100.0%	60		

At 24 hours, analysing the pain scores revealed the donor site to be painful in 2 patients in bupivacaine group. The saline group reported pain in 9 patients at this time. This difference was statistically significant with p value =0.020.

Thus, in bupivacaine group only 2 patients(6.7%) required rescue analgesia in form of tramadol. This percentage was higher in saline group comprising 30 % patients.

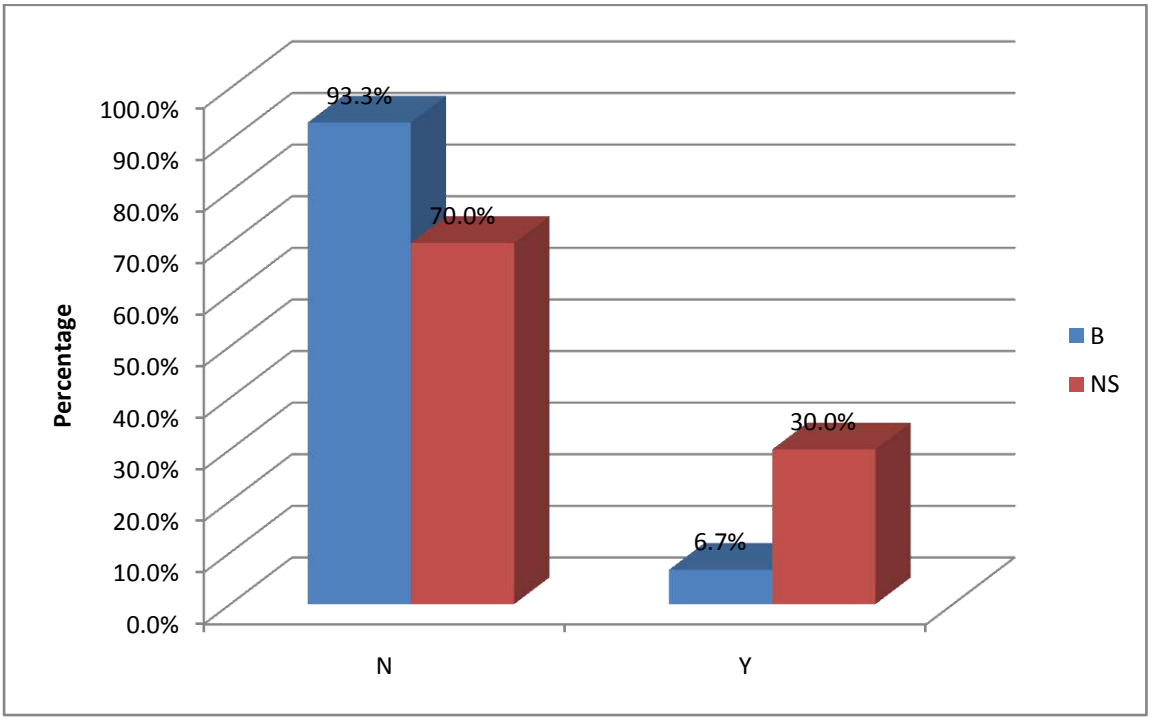


FIGURE 14: DONOR SITE PAIN AT 24 HOURS AND RESCUE ANALGESIA

TABLE 15: FINAL ASSESSMENT OF PAIN AND RESCUE ANALGESIA REQUIREMENT

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
FINAL ASSESSMENT	No	25	83.3%	3	10.0%	28	32.411	0.000
	Yes	5	16.7%	27	90.0%	32		
Total		30	100.0%	30	100.0%	60		

The final assessment showed that, during study period of 24 hrs in bupivacaine group, 5 patients had reported donor site pain with pain score >4 (16.7%) while 25 patients (83.3%) had no pain. So, in bupivacaine group only 5 patients had received rescue analgesia during first 24 hours. But in saline group, 27 patients had donor site pain during the first 24 hrs and received rescue analgesia in form of tramadol. Only 3 patients out of 30 in saline group required no rescue analgesia.

The final assessment showed a statistically significant difference in pain reported by patients in both groups and thus in number of patients requiring rescue analgesia.

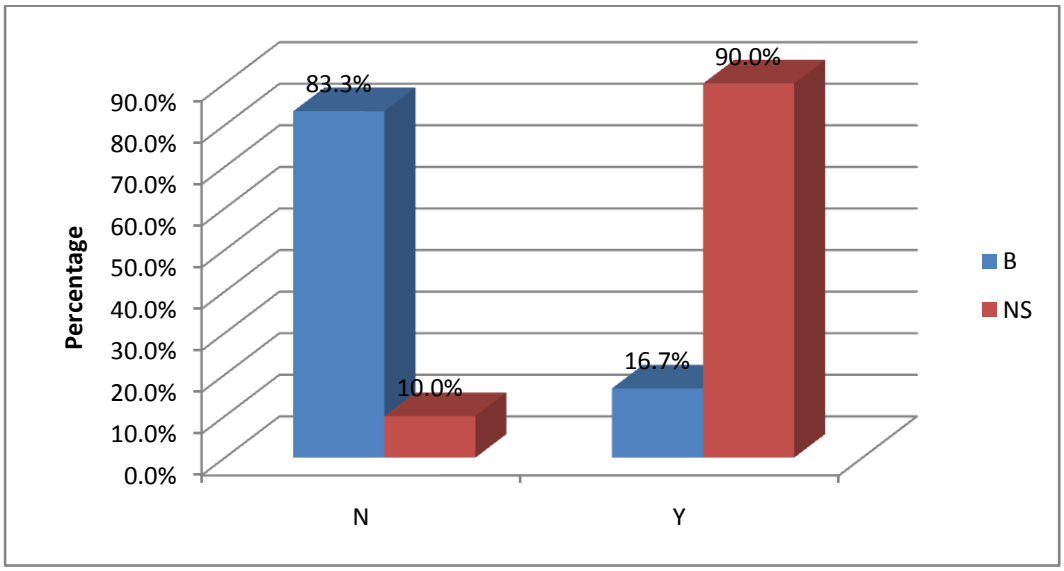


FIGURE 15: FINAL ASSESSMENT OF PAIN AND RESCUE ANALGESIA REQUIREMENT

TABLE 16: COMPARING MEAN PAIN SCORES IN BOTH GROUPS

PAIN SCORES	B		NS		t	p-value	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
8 HRS	1.30	1.66	4.00	2.15	-5.440	0.000	-3.693	-1.707
16 HRS	1.60	1.10	4.93	1.80	-8.654	0.000	-4.104	-2.562
24 HRS	1.57	1.55	3.10	1.69	-3.668	0.001	-2.370	-0.696

In Bupivacaine group, the mean of the pain scores reported was 1.30 at 8 hrs compared to 4.00 in the saline group. This difference in the pain scores was statistically significant.

Similarly, at 16 hours assessment showed Bupivacaine group to have lower mean pain score than the saline group with statistical significance.

The reported pain scores in saline group at 24 hrs showed a mean of 3.10 whereas the mean in bupivacaine group was 1.57. At 24 hrs also the difference in pain scores was statistically significant.

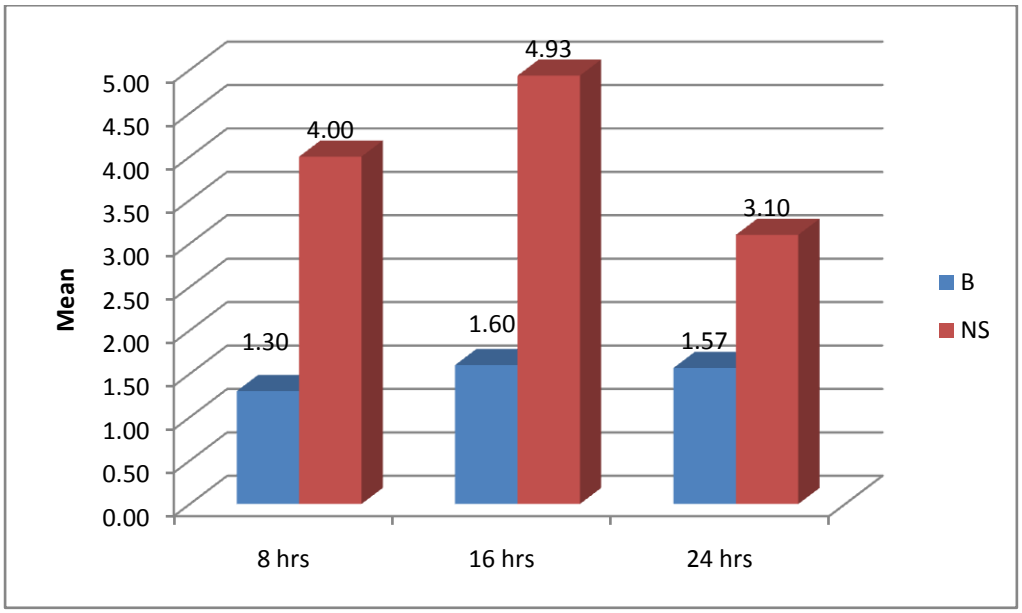


FIGURE 16: COMPARING MEAN PAIN SCORES IN BOTH GROUPS

TABLE 17: REPORTED ADVERSE EFFECTS IN STUDY

ADVERSE EFFECT	No. of cases	Percentage
BURNING SENSATION	1	1.7%
PAIN	2	3.3%
TINGLING	5	8.3%
NIL	52	86.7%
Total	60	100.0%

No advserse effect was reported in majority of the study population. Commonest observed effect was tingling sensation on administration at donor site. 1 patient had complained of burning sensation and 2 patients reported pain. However, these adverse effects were not bothersome to the patient and subsided in few minutes.

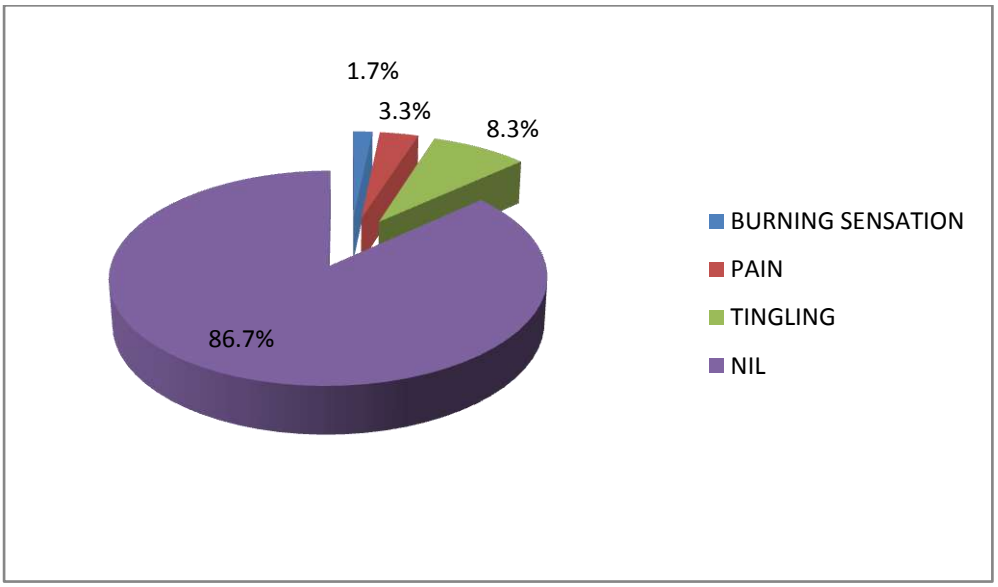


FIGURE 17: REPORTED ADVERSE EFFECTS IN STUDY

TABLE 18: COMPARING ADVERSE EFFECTS IN BOTH GROUPS

		BUPIVACAINE/NORMAL SALINE INSTILLATION				Total	Chi-square value	p-value
		B		NS				
ADVERSE EFFECT	BURNING SENSATION	1	3.3%	0	0.0%	1	3.277	0.351
	PAIN	0	0.0%	2	6.7%	2		
	TINGLING	2	6.7%	3	10.0%	5		
	NIL	27	90.0%	25	83.3%	52		
Total		30	100.0%	30	100.0%	60		

No adverse effect was noted in majority of patients. One patient reported of burning sensation on administration of bupivacaine. Two patients complained of pain while giving saline through the catheter. But this effect was transient and subsided in few minutes. Also, this had no statistical significance.

The commonest adverse effect observed was tingling sensation present in 2 patients in bupivacaine group and 3 in saline group. This difference had no significance statistically.

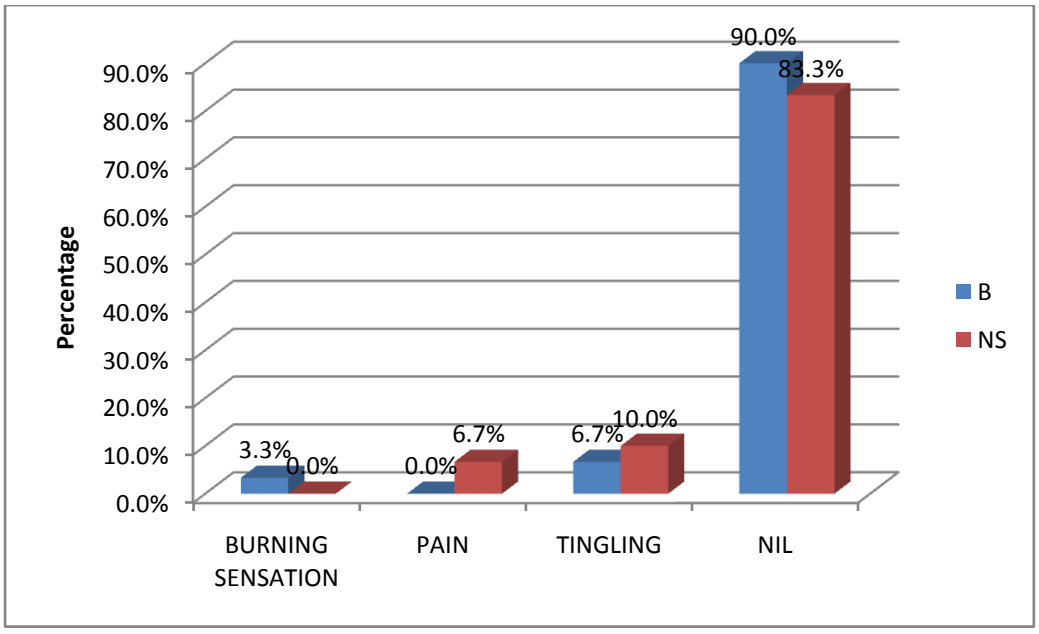


FIGURE 18: COMPARING ADVERSE EFFECTS IN BOTH GROUPS

DISCUSSION

Skin grafting is a commonly performed surgical procedure for soft tissue defect reconstruction. There are numerous applications making it valuable not only to plastic and reconstructive surgeons but also to various other surgical specialties as well.[4]

A split thickness skin graft comprises of epidermis and superficial dermis. After harvesting split-thickness skin graft, a new iatrogenic partial thickness wound is created called the donor site.[10]

STSG, although being standard of care for full thickness burn wounds and other reconstructive procedures, numerous complications such as impaired healing, infection, excessive pain, scarring, pruritus and either hypopigmentation or hyperpigmentation, are commonly reported on the donor site.[11]

Donor site pain is one of the most distressing symptoms that has been reported by the patients, especially in the early postoperative period. Donor site creates painful iatrogenic wounds due to exposure of free nerve endings in dermis. These stimulate pain receptors in the dermis and these pain signals are then transmitted to the central nervous system by afferent fibers in the cutaneous nerves supplying the harvested site.[14]

Often, the donor site is reported by the patients to be more painful than the recipient site. This pain has a great effect on the post operative course and thus, patient's overall recovery. This has significant affect on early mobilization, causes reduced sleep and an increased need for analgesics postoperatively.[16]

For alleviation of this donor site pain, use of analgesics such as morphine or morphine-like substances is very frequent and that too in higher dosages. Unfortunately, this systemic use of opioids can cause many adverse effects like nausea, vomiting, pruritus, constipation, urinary retention and more fatal adverse effects such as respiratory depression. The prolonged use of opioids can also produce tolerance to the drug and hyperalgesia. Such complications may eventually

cause additional treatment challenges and longer stays in the hospital.[19,20]

Paraffin gauze dressing has been traditionally used for coverage of donor sites worldwide. It's a kind of a semi-occlusive, dry, non-absorbent, adherent dressing. This dressing is very commonly applied by most surgeons for donor site coverage but major drawback of such dressing is pain over the donor site.

Despite an abundance of literature on wound dressings, no consensus has been reached on dressings or methods which optimize management of post harvest donor site pain.[27] Alleviation of donor site pain can be done by a variety of approaches including continuous local anesthetic infusion, subcutaneous anesthetic injections, application of topical agents, wound dressings such as collagen, hydrocolloids and other non pharmacological measures.

After the review of literature on abundance of dressing materials and techniques, we realized that there was no conclusive evidence regarding the superiority of a dressing method for donor site pain relief.

Donor site pain as discussed is one of the most distressing symptoms reported by the patients in the early postoperative period and perhaps is most disturbing complication. The graft harvest exposes free nerve endings and these stimulate the pain receptors and transmit pain to central nervous system. This causes significant morbidity, prolongs recovery and increases the need for analgesics.

So the combined effect of consequences of donor site pain and use of higher doses of analgesics and their adverse effects have a major effect on overall outcome associated with this procedure.

Our study was conducted in the Department of Plastic and Reconstructive surgery, Dayanand Medical College and Hospital, Ludhiana from the year 2017-2019. The study was done with the aim to compare the efficacy of 0.125 % bupivacaine moistened dressing and conventional saline dressing for STSG donor site pain relief and to note any adverse effects with the use of bupivacaine.

The basis of our study was that local anaesthetic agent bupivacaine should result in pain relief at donor site as it potentially blocks the nerve

endings and thus, in process inhibits the transmission of pain signals to the brain.

Wiechula [38] had compared moist dressings to non moist dressings in his analysis. He evaluated 58 randomised control trials and intra individual studies and found moist dressings decreased the days needed for healing and were associated with lower pain scores. The findings of Voineskos et al [27] were consistent with Wiechula's review, majority of moist dressings were associated with less pain.

Keeping in view of the findings in the literature suggesting that moisture promotes wound healing and has lower pain, in both the groups in our study, moistened dressings were used.

Bupivacaine is an amide anesthetic agent that acts by blocking the nerve impulses transmitting pain sensation to the brain. It is most commonly used for spinal blocks but it also finds its application in local infiltration and for peripheral nerve blocks.[28]

A study done in 1989 by Chester et al consisted of thirty patients undergoing cholecystectomy. The patients received 0.5% bupivacaine for wound perfusion for first 24 hours and this was followed by Normal saline perfusion for next 24 hrs or the other way round i.e receiving normal saline first and 0.5% bupivacaine in later 24 hrs. Chester et al noticed a lower pain score with bupivacaine, along with less number of bolus dosages for pain on the day of bupivacaine use. So, concluded that surgical wounds on bupivacaine perfusion have better pain relief than saline.[93]

In another study by Kadar et al, after tonsillectomy, packing of the right tonsillar fossa was done with 0.5 % bupivacaine solution soaked gauze and left fossa as control with gauze soaked in 0.9 % normal saline. They observed bupivacaine on topical application reduces post operative site pain.[94]

Zohar et al. from Tel Aviv University studied the role of bupivacaine for pain relief in 36 patients after total abdominal hysterectomy and bilateral salpingooophorectomy and found that group where bupivacaine was used, required less of rescue analgesia.[95]

In a study by Goldstein et al from Paris, the role of local anesthetics in preventing postoperative pain after laparoscopic gynecologic surgery was studied. They found that analgesia (morphine) requirement was considerably less in bupivacaine group than normal saline group.[96]

After harvesting bone graft from anterior iliac crest, many patients reportedly feel severe pain at the donor site. In their study in 2006-2007, Barkhuysen et al studied the effect of single dose of bupivacaine for the pain relief at site of harvest. They observed no difference in the post operative pain between the bupivacaine and the control group.[97]

The study done by Hernandez et al in 2011-2012 administered local anesthetic agent bupivacaine as a continuous infusion to manage the pain at STSG donor site. They noted a substantial reduction in worst, least, and average donor site pain scores.[98]

Similarly, Gamli et al in 2012 did a study and found that the patients in whom the bupivacaine soaked gelfoam was placed at iliac crest harvest site, a decrease in post operative analgesia usage was found. But there was no significant difference observed in visual analogue scale scores for pain.[99]

Thus, after reviewing these studies we decided that bupivacaine can be used as a viable option for donor site pain relief.

Our next concern was regarding the adverse effects due to its use. The local anaesthetics are associated with adverse effects at toxic concentrations in plasma. The dreaded complication with bupivacaine is cardiotoxicity.

In the study done by R. Alvi et al assessed safety of depot preparations of bupivacaine and ketoprofen on application over donor site of STSG. Mean levels of bupivacaine obtained were 0.07 pg/ml (range 0.03-0.1).Toxic serum level for bupivacaine have been reported to be 4ug/ml. They concluded that possibility of such preparations on application at denuded dermis resulting in toxic levels is quite unlikely.[100]

Fischer et al conducted a study in 2003 to determine the safety of bupivacaine infiltration subcutaneously over donor site for STSG harvest. The average age in study was 14.3 years. The administered

dose of bupivacaine was significantly lower than 3mg/kg. They observed that highest levels of bupivacaine obtained were well below the safe upper limit in children. Also, no signs of toxicity were noted.[18] Thus, these studies showed us that it is unlikely that the bupivacaine application topically results in toxic concentrations in plasma.

In our study considering safety profile, firstly all patients having any cardiac history were excluded from the study. Any patient with history of allergy to local anaesthetic was also excluded. The study population was between 10 -60 years.

Also, 0.125 % bupivacaine was used in our study. This is an even lower concentration of bupivacaine. In study performed in Nigeria, Oluwatosin and his colleagues used 0.5% aqueous solution of bupivacaine hydrochloride for application to donor site of split thickness skin graft.[103] The similar study done in 2000-2001 in Thailand by Jenwitheesuk et al, dressings moistened with bupivacaine 0.5% in dose of 6 ml per 100 cm^2 of donor site area were used.[104]

Muhammad Raza et al used dressing at skin graft donor site soaked with 0.25% bupivacaine solution and compared this with saline moistened dressings. The patients were divided in two groups, A and B, and each group comprised of 75 patients. For every 100 cm^2 of the donor site area calculated, 12 mL of 0.25% bupivacaine was administered immediately after surgery and this was repeated after 12 hours. In the other group, saline moistened dressings were used. For every 100 cm^2 of donor site area, 12 ml of saline was instilled and this was repeated after 12 hours of first instillation.[105]

So, we conducted our study to evaluate the efficacy of 0.125% bupivacaine for donor site pain relief and also report any adverse effects.

The present study included two groups with 30 patients in each group. In Bupivacaine group, for every 100 cm^2 of donor area, 12 ml of 0.125% bupivacaine was used and this was repeated after 12 hrs. In saline group, normal saline was used to moisten the donor site dressing. For 100 cm^2 donor site area, 12 ml of saline was instilled once immediately after surgery and repeated after 12 hours.

Thigh was chosen as the donor site. Jeffrey et al did a study to search the ideal site for split thickness skin graft donor site in 2014. They gave a detailed account about the quality of ideal donor site and concluded thigh as the ideal donor site.[35]

Worldwide paraffin gauze is most commonly used for donor site dressing. So, we used this widely available dressing with slight modification by adding saline or 0.125 % bupivacaine to keep it moist.

Our study included 46 males and 14 females. In the bupivacaine group, out of 30 patients 5 were females and 25 males. Similarly, the saline group comprised of 9 females and 21 males. Both the groups were demographically similar in gender distribution.

Also, mean age in bupivacaine group was 34.83 years. In NS group the mean age was 33.40 years. This difference was not statistically significant. Thus, both the groups were comaparable with respect to age distribution. In study by Muhammad Raza et al[105], mean age in bupivacaine group was 32.79 years while in saline group it was 31.83 years. However, the mean age in study by Jenwitheesuk et al[104] was 41 years in bupivacaine group and 31 years in saline group.

In majority of our study population, no associated illness was found. Commonest comorbidity was diabetes mellitus.

The commonest mode of injury necessitating skin grafting was burns in both the groups.

The two groups showed no statistical difference with regards to type of anaesthesia used for the procedure. The bupivacaine group comprised of 23 patients operated under GA while 22 patients were administered GA in saline group. The previous studies show no data on the type of anaesthesia used in procedure associated with graft harvest.

Thigh was chosen as the donor site and two groups were similar in respect to side chosen for harvest.

The study revealed that mean donor site area in Bupivacaine group was 289.2 cm^2 and in saline group 352.27 cm^2. The quantity of bupivacaine instilled to keep the donor site moist showed a mean of 34.70 ml compared to 42.24 in the NS group. These differences b/w donor areas and quantities instilled showed no statistical significance

with p value= 0.276. Thus, our study groups were comparable in terms of donor site area and quantities of the instilled agents. The maximum dose of bupivacaine that can be safely administered is 2mg/kg. Considering reference weight as 60 kg, maximum amount of bupivacaine safely administered is 120 mg. In 0.125 % bupivacaine group, the maximum surface area of donor site was 750 cm^2 and 90 ml of this was instilled. This is 112.5 mg of bupivacaine, which is below the safe upper limit.

Jenwithseeuk et al[104] in their study reported the donor site areas in bupivacaine group and saline group as 295 and 225 cm^2 respectively.

Our result analysis revealed that out of 30 patients receiving bupivacaine instillation to keep donor site moist , pain was reported by 3 patients with pain score >4 at 8 hours post instillation. In NS group, the donor site was painful in 17 patients. Thus, at 8 hours, 10% patients in Bupivacaine group had pain at donor site and required rescue analgesia. The NS group reported donor site pain in 56.7% patients. This difference was statistically significant.

Analysis at 16 hours showed that donor site pain (with pain score >4) was present in 3.3 % patients in bupivacaine group and in 73.3% patients in the NS group. So, just 1 patient required rescue analgesia in bupivacaine group compared to 22 patients in NS group. This difference in number of patients reporting pain and requiring rescue analgesia at 16 hours was found to be statistically significant.

At 24 hours, pain at donor site was reported by 2 patients out of 30 in the bupivacaine group compared to 9 out of 30 in the NS group. So, 6.7% patients in bupivacaine group received rescue analgesia at 24 hours in bupivacaine group as compared to 30% in NS group. This difference held statistical significance with p value=0.020

Our final assessment after 24 hours showed that during 24 hour study, donor site pain was reported by 5 patients out of 30 in the bupivacaine group. Thus, 16.7 % patients in this group had pain at donor site of STSG in the bupivacaine group. So, just 5 patients out of 30 received rescue analgesia in form of tramadol in the bupivacaine group.

In NS group during 24 hours, our analysis showed that 27 patients out of 30 had required rescue analgesia in the first 24 hours. The donor site pain was present in 90 % of the patients and 90 % patients required rescue analgesia. This difference in number of patients reporting donor site pain and thus, requiring rescue analgesia in form of tramadol in first 24 hours after STSG held statistical significance proved by p value<0.05.

Since reduction in need for rescue analgesia is equivalent to effectiveness, 25 out of 30 patients in bupivacaine group did not require rescue analgesia gave 83.3% effectiveness of bupivacaine moistened dressing in reduction of postoperative pain at STSG donor site. In NS group, only 3 out of 30 patients didn't require rescue analgesia which gives 10 % effectiveness of conventional dressing in reducing pain at STSG donor site. So, 0.125% bupivacaine moistened dressing was effective in post operative pain reduction at STSG donor site.

The study by Muhammad Raza et al[105] compared instilling 0.25% bupivacaine and saline for pain relief at donor site. They instilled 12 ml of 0.25% bupivacaine for every 100 cm^2 of the donor site area calculated once immediately after surgery and this was repeated after 12 hours. In the other group, saline moistened dressings were used. For every 100 cm^2 of donor site area, 12 ml of saline was instilled and this was repeated after 12 hours of first instillation. In bupivacaine group, only 5 patients out of 75 required rescue analgesia making it around 6.7%. In Saline group, 72 out of 75(96%) patients required rescue analgesia.

A higher percentage of patients required rescue analgesia in our study as compared to the study by Raza et al. But the results obtained in our study were statistically significant. And we obtained these significant results by using an even smaller concentration of Bupivacaine (0.125% bupivacaine) creating further enhancement of the safety profile of the local anaesthetic agent. Also, this smaller, safer yet effective concentration of bupivacaine permits pain relief of even larger donor areas.

The pain scores in our study had a mean of 1.30, 1.60 and 1.57 at 8, 16 and 24 hours respectively in the bupivacaine group. In saline group, the mean pain scores were 4, 4.93 and 3.10 at 8, 16 and 24 hours respectively. Patients receiving 0.125 % Bupivacaine instillation had consistently lower pain scores with statistical significance during the study duration.

Jenwitheesuk et al[104] in their study conducted for donor site pain relief used 0.5 % bupivacaine for moistening the donor site dressings. They instilled 6 ml/ 100 cm^2 every 12 hours. The other group received saline moistened dressing with saline 6 ml/100cm^2 instilled in same method and intervals. They reported that means of pain scores were lower in the group receving 0.5 % bupivacaine. The findings of our study were consistent with those of this study, at a concentration being one fourth.

There was no adverse effect observed in majority of our study population. Commonest observed effect in our study was tingling sensation reported by 2 patients in bupivacaine group compared to 3 in the NS group. 1 patient reported a burning sensation on bupivacaine instillation. Two patients had complained of pain after saline instillation. However, all these effects although noticed in a small study population were transient and subsided in few minutes without causing any major discomfort to the paitient. Jenwithseeuk et al reported in their study that four patients had pain during bupivacaine administration for 3-5 minutes.[104]

So, even at such lower Bupivacaine concentration (0.125%) we observed a reduction in pain at the donor site of STSG. This pain relieving effect was statistically significant on comparing with the saline group. Previous studies had reported similar results, but with a higher bupivacaine concentration (0.5% by Jenwitheesuk et al and 0.25% by Raza et al).

Also with this 0.125% bupivacaine application, there was a significant decrease in rescue analgesia requirement. This ensured a reduction in the possible adverse effects with frequent and higher use of analgesics such as opioids. Also, this reduction implied a lower treatment cost.

This smaller concentration also enabled its application over larger donor site areas.

All this ensured a comfortable, pain free recovery for the patient.

Although donor site infection was not a part of our study, we did not find donor site in any patient getting infected. We attribute this to our strict aseptic technique during graft harvest, antibiotic coverage and maintaining this strict asepsis during instillation of bupivacaine or saline.

LIMITATIONS OF STUDY: small sample size

SUMMARY AND CONCLUSION

This randomized, prospective, comparative study was conducted in the Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital, Ludhiana over a two year period with aim to compare the efficacy of 0.125% bupivacaine moistened dressing and conventional dressing for pain relief on split thickness skin graft donor site and to report any adverse effects.

All patients, in age group 10-60 years and thigh as donor site, undergoing split thickness skin grafting and willing to participate in the study were included. The patients with history of allergy to local anaesthetics or having any cardiac history were excluded from the study.

The patients were randomly divided into two groups with 30 cases in each group. The donor site dressing was done by a standardized protocol described in the material and methods. In Group A(Bupivacaine group), the donor site dressing was moistened by instilling an aqueous solution of 0.125% bupivacaine hydrochloride through the catheter under all aseptic techniques. For every 100 cm^2 of the donor site wound, 12 ml of bupivacaine solution was instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

In Group B (NS group), the donor site dressing was kept soaked by instilling normal saline through the catheter under all aseptic conditions. Just like Group A, in Group B for every 100 cm^2 of the donor site wound 12 ml of the normal saline was instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

For the assessment of pain, patients were interviewed for pain using Visual Analogue Scale (VAS) every 8 hours by an independent observer. Patients with complains of pain or in whom pain score was more than 4 (i.e. need for analgesia), were given intravenous (IV) analgesia in the form of tramadol.

The two groups were comparable with respect to gender distribution, mean age, mode of injury, type of anaesthesia, donor site area and quantity of solutions instilled.

At 8 hours post instillation, in the bupivacaine group, 27 patients reported no pain at donor site while 3 patients had pain at donor site(pain score >4). The saline group comprised of 17 patients who reported the donor site to be painful (pain score > 4). This difference was statistically significant with a p value = 0.000

The assessment at 16 hours revealed the donor site to be painful (pain score >4) in 1 patient among 30 in the bupivacaine group. In the saline group, the donor site pain was reported by 22 patients. This was statistically significant ($p< 0.05$)

At 24 hours, analyzing the pain scores revealed the donor site to be painful in 2 patients in bupivacaine group. The saline group reported of pain in 9 patients at this time. This difference was statistically significant with p value =0.020.

The final assessment after 24 hours showed that in bupicaine group, 5 patients had reported donor site pain with pain score >4 (16.7 %) while 25 patients (83.3%) had no pain. So, in bupivacaine group only 5 patients had received rescue analgesia for pain relief in first 24 hours. But in saline group, 27 patients (90%) had donor site pain during the first 24 hrs and received rescue analgesia in form of tramadol. This difference was statistically significant. In Group A (Bupivacaine group), 25 out of 30 (83.3%) patients did not require rescue analgesia. In Group B (NS group), 3 out of 30 (10%) patients didn’t require rescue analgesia. There was 83.3% effectiveness of bupivacaine soaked dressing while only 10% effectiveness of conventional dressing in our study.

The mean pain scores were consistently lower in the bupivacaine group compared to saline group.

The commonest adverse effect seen was tingling sensation in 5 patients, 2 in bupivacaine group and 3 in the saline group. This effect was transient and subsided in few minutes. No intervention was required for this.

It was evident that 0.125% Bupivacaine moistened dressing was effective in donor site pain relief. However, further studies with larger number of subjects, including rate of healing at donor site and assessment of pain relief for longer duration may be considered.

Thus, we can conclude that 0.125% Bupivacaine moistened dressing is effective in providing pain relief at STSG donor sites as compared to conventional saline dressings. No serious or bothersome adverse effects were reported due to the instillation of any agent.

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Picture 1: Measuring donor site length(in centimetres) after complete hemostasis

Picture 2: Measuring donor site width (in centimetres) after complete hemostasis

Picture 3: Placement of catheter longitudinally over donor site

Picture 4: Covering catheter with abundant sterile gauzes

Picture 5: Donor site dressing with sterile bandage

Picture 6: Complete dressing with crepe bandage and position of catheter for instillation

SR NO	NAME	AGE	SEX	MRD NO	PAST HISTORY	H/O ALLERGY TO LOCAL ANAESTHETICS	ASSOCIATED ILLNESS	WOUND HISTORY		TYPE OF ANAESTHESIA	DONOR SITE (THIGH)	DONOR AREA DIMENSIONS(CM2)	TIMING OF BUPIVACAINE/NORMAL SALINE INSTILLATION						PAIN SCORE			FINAL ASSESSMENT AT 24 HRS (Requirement for Pain		
								MODE OF ONSET	DURATION(				DOSE		TIME		QUANTITY(ML)	ADVERSE EFFECT	8 HRS	16 HRS	24 HRS	8 HRS	16 HRS	24 HRS
													1ST	AFTER 12 HRS										
1	PK	45	F	443559	NOT SIG	NIL		RSA	5	SA	LEFT	462	NS	NS	2PM	2AM	55	NIL	6	5	2	Y	N	N
2	KS	66	M	124784	NOT SIG	NIL		SPONT	5	SA	LEFT	262	B	B	11AM	11PM	31.5	NIL	0	0	2	N	N	N
3	HK	20	F	451449	NOT SIG	NIL	HYDROPNEUMOTHORAX TRAUMA	RSA	45	GA	LEFT	240	B	B	2PM	2AM	28.8	NIL	0	0	0	N	N	N
4	VT	40	M	484117	NOT SIG	NIL		RSA	5	SA	RIGHT	100	NS	NS	2PM	2AM	12	NIL	0	2	5	N	N	Y
5	A	11	F	510381	NOT SIG	NIL		BURN(SCALD)	365	GA	LEFT	121	B	B	2PM	2AM	14.5	TINGLING	0	1	0	N	N	N
6	BS	50	M	502118	NOT SIG	NIL		SPONT	45	SA	RIGHT	100	NS	NS	3PM	3AM	12	NIL	2	5	5	N	Y	Y
7	RK	30	F	422142	NOT SIG	NIL		BURN(ACID)	1460	GA	LEFT	182	B	B	12PM	12AM	21.8	NIL	0	2	2	N	N	N
8	JS	51	M	502486	NOT SIG	NIL		BURNS(ELECTRIC)	60	GA	LEFT	500	B	B	12PM	12AM	60	TINGLING	0	0	2	N	N	N
9	GS	30	M	511332	NOT SIG	NIL	DRUG ADDICT	BURNS(FLAME)	45	GA	LEFT	360	B	B	12PM	12AM	43.2	NIL	5	2	2	**Y**	N	N
10	MS	17	M	488993	NOT SIG	NIL		BURNS(ELECTRIC)	90	GA	LEFT	300	NS	NS	7PM	07:30AM	36	PAIN	0	2	2	**N**	N	N
11	AS	21	M	540039	NOT SIG	NIL	HEMORRAGIC CONTUSIONS	RSA	2	GA	RIGHT	100	B	B	12PM	12AM	12	NIL	0	2	1	N	N	N
12	SS	20	M	533752	NOT SIG	NIL		MACHINE INJURY	13	GA	LEFT	105	B	B	12PM	12AM	12.6	NIL	2	0	2	N	N	N
13	RS	35	M	530705	NOT SIG	NIL		RSA	15	GA	LEFT	255	B	B	2PM	01:30AM	30.6	NIL	5	1	2	**Y**	N	N
14	JS	51	M	502486	NOT SIG	NIL		BURNS(ELECTRIC)	70	GA	RIGHT	500	NS	NS	2PM	2AM	60	NIL	1	5	2	N	Y	N
15	HS	14	M	538370	NOT SIG	NIL		DOG BITE	20	GA	LEFT	375	B	B	11:45AM	11:45PM	45	NIL	0	2	0	N	N	N
16	PK	35	M	541282	NOT SIG	NIL		RSA	20	GA	RIGHT	156	B	B	2PM	01:50AM	18.7	NIL	2	2	2	N	N	N
17	G	25	M	528958	NOT SIG	NIL		BURNS(ELECTRIC)	45	GA	RIGHT	240	NS	NS	11:45AM	11:40PM	28.8	NIL	5	2	2	Y	N	N
18	TR	50	F	557075	NOT SIG	NIL	L2, RIGHT TIBIA FRACTURE	RSA	5	GA	LEFT	300	NS	NS	11:30AM	11PM	36	NIL	2	5	1	N	Y	N
19	MS	21	M	566821	NOT SIG	NIL	EYEBROW LACERATION	RSA	1	GA	RIGHT	165	NS	NS	09:30AM	09:30PM	19.8	PAIN	2	6	2	N	Y	N
20	PK	24	F	561548	NOT SIG	NIL		SPONT	20	SA	RIGHT	120	NS	NS	10AM	10PM	14.4	NIL	2	5	3	N	Y	N
21	GS	29	M	577318	NOT SIG	NIL		BURNS(THERMAL)	2920	SA	LEFT	210	B	B	4PM	4AM	25.2	NIL	0	2	2	N	N	N
22	JS	36	M	571708	NOT SIG	NIL		BURNS(ELECTRIC)	12	GA	RIGHT	500	NS	NS	1PM	1AM	60	NIL	5	6	3	Y	Y	N
23	KS	24	M	568424	NOT SIG	NIL		BURNS(ELECTRIC)	20	GA	LEFT	450	B	B	12:20PM	12:20AM	54	NIL	0	3	2	N	N	N
24	JS	36	M	571708	NOT SIG	NIL		BURNS(ELECTRIC)	74	GA	RIGHT	320	B	B	3PM	03:30AM	38.4	NIL	2	2	0	N	N	N
25	MR	59	M	579698	NOT SIG	NIL	ASTHMA	BURNS(FLAME)	30	GA	LEFT	690	NS	NS	11AM	11PM	82.8	NIL	3	2	6	N	N	Y
26	HS	13	M	587576	NOT SIG	NIL		BURNS(ELECTRIC)	30	GA	LEFT	550	NS	NS	6PM	6AM	66	NIL	6	5	2	Y	Y	N
27	SD	32	F	663965	NOT SIG	NIL		BURNS(FLAME)	10	GA	RIGHT	750	NS	NS	1PM	01:10AM	90	NIL	2	7	5	N	Y	Y
28	GS	45	M	601097	NOT SIG	NIL	DM,HTN	TRAUMA	45	SA	RIGHT	100	B	B	12:40PM	12:20AM	12	NIL	2	3	0	N	N	N
29	HS	13	M	587576	NOT SIG	NIL		BURNS(ELECTRIC)	40	GA	RIGHT	750	NS	NS	1PM	1AM	90	TINGLING	6	7	5	Y	Y	Y
30	AK	44	M	607445	NOT SIG	NIL		MACHINE INJURY	17	GA	RIGHT	80	B	B	11:30AM	11:30PM	9.6	NIL	2	2	0	N	N	N
31	NS	56	M	610071	NOT SIG	NIL	DM,HCV	RSA	15	SA	RIGHT	195	B	B	12:15PM	12:10AM	23.4	NIL	2	2	0	N	N	N
32	NS	55	M	631222	NOT SIG	NIL	L1 FRACTURE PLATING	BURNS(SCALD)	20	LA	LEFT	120	B	B	10AM	10PM	14.4	NIL	0	2	1	N	N	N
33	M	42	M	627133	NOT SIG	NIL		BURNS(FLAME)	22	SA	LEFT	500	NS	NS	01:45PM	01:30AM	60	NIL	6	5	3	Y	Y	N
34	GS	45	M	643867	NOT SIG	NIL		BURNS(ELECTRIC)	9	GA	LEFT	300	B	B	11:15AM	11:00PM	36	NIL	0	2	2	N	N	N
35	S	29	M	644013	NOT SIG	NIL		BURNS(FLAME)	9	GA	LEFT	525	NS	NS	01:30PM	01:15AM	63	NIL	5	5	2	Y	Y	N
36	SK	11	M	642961	NOT SIG	NIL		TRAUMA	15	GA	RIGHT	117	NS	NS	11:55AM	12:00PM	14.04	NIL	3	2	2	N	N	N
37	KL	56	M	625275	NOT SIG	NIL		BURNS(ELECTRIC)	51	GA	RIGHT	408	B	B	06:30PM	07:30AM	48.96	NIL	6	2	3	Y	N	N
38	PS	45	M	653655	NOT SIG	NIL		TRAUMA	16	GA	RIGHT	150	B	B	11:30AM	11:15PM	18	NIL	2	1	0	N	N	N
39	JS	35	M	659858	NOT SIG	NIL		TRAUMA	10	SA	LEFT	160	B	B	12PM	12AM	19.2	NIL	2	1	2	N	N	N
40	S	29	F	644013	NOT SIG	NIL		BURNS(FLAME)	33	GA	RIGHT	500	NS	NS	02:30PM	2AM	60	NIL	5	6	1	Y	Y	N
41	AS	47	M	657540	NOT SIG	NIL	DM	ASSAULT	12	GA	RIGHT	150	NS	NS	12:00PM	11:45AM	18	NIL	5	6	2	Y	Y	N
42	S	48	F	667732	NOT SIG	NIL	DM	TRAUMA	40	GA	RIGHT	110	B	B	1PM	1AM	13.2	NIL	0	2	1	N	N	N
43	MS	28	M	692118	NOT SIG	NIL	ULNA FRACTURE LEFT, RADIAL A, ULNAR, MEDIAN N	RSA	19	GA	RIGHT	120	NS	NS	3PM	2:30 AM	14.4	NIL	5	5	2	Y	Y	N
44	PS	52	M	701170	NOT SIG	NIL		RSA	16	SA	RIGHT	180	NS	NS	2PM	2AM	21.6	NIL	5	5	2	Y	Y	N
45	JS	29	M	717570	NOT SIG	NIL	LEFT LATERAL MALLEOLUS FRACTURE	RSA	9	SA	RIGHT	300	B	B	3:40 PM	3:15AM	36	NIL	0	1	0	N	N	N
46	BK	54	F	720699	NOT SIG	NIL	HTN	RSA	40	GA	LEFT	120	NS	NS	2:30PM	2:30 AM	14.4	NIL	6	2	5	Y	N	Y
47	AK	18	F	715486	NOT SIG	NIL		RSA	13	GA	LEFT	99	NS	NS	1:30PM	1:30AM	11.8	NIL	6	7	5	Y	Y	Y
48	AS	22	M	705151	NOT SIG	NIL	LEFT BELOW ELBOW AMPUATAION	BURNS(ELECTRIC)	30	GA	RIGHT	600	B	B	7PM	7AM	72	NIL	2	2	1	N	N	N
49	PR	30	M	726989	NOT SIG	NIL		BURNS(ELECTRIC)	6	GA	LEFT	225	B	B	12:30PM	12:30AM	27	BURNING SENSATI	1	0	6	N	N	Y
50	GS	22	M	737933	NOT SIG	NIL	OPEN FRACTURE TIBIA LEFT	RSA	30	SA	RIGHT	120	NS	NS	4:45PM	5:00AM	14.4	NIL	2	2	3	N	N	N
51	AS	42	M	732457	NOT SIG	NIL		BURNS(FLAME)	30	GA	RIGHT	550	B	B	11AM	11PM	66	NIL	2	5	6	N	Y	Y
52	R	28	M	732446	NOT SIG	NIL	SEIZURE DISORDER	BURNS(SCALD)	118	GA	RIGHT	480	NS	NS	1PM	1AM	57.6	NIL	2	6	6	N	Y	Y
53	SS	15	M	758970	NOT SIG	NIL		RSA	20	GA	LEFT	750	B	B	11AM	11PM	90	NIL	2	0	3	N	N	N
54	GK	30	F	749395	NOT SIG	NIL		BURNS(FLAME)	525	GA	RIGHT	96	NS	NS	1PM	1AM	11.5	NIL	2	6	3	N	Y	N
55	SB	52	M	748089	NOT SIG	NIL	H/O FACIAL PALSY	BURNS(FLAME)	20	GA	LEFT	810	NS	NS	2PM	2AM	97.2	TINGLING	6	7	2	Y	Y	N
56	SD	26	M	736019	NOT SIG	NIL	LEFT PELVIC FRACTURE	RSA	37	SA	LEFT	960	NS	NS	1PM	1AM	115	NIL	8	7	7	Y	Y	Y
57	R	38	F	701248	NOT SIG	NIL	GRADE 2 SACRAL SORE	BURNS(FLAME)	96	GA	LEFT	572	B	B	12PM	12AM	68.6	NIL	0	2	2	N	N	N
58	RA	12	M	688719	NOT SIG	NIL	AML	SPONTANEOUS	30	GA	LEFT	132	NS	NS	12PM	12AM	15.8	NIL	6	7	2	Y	Y	N
59	MS	18	M	488993	NOT SIG	NIL		BURNS(ELECTRIC)	365	GA	LEFT	420	B	B	1PM	1AM	50.4	NIL	0	2	1	N	N	N
60	ND	46	F	287302	NOT SIG	NIL		RSA	12	GA	LEFT	132	NS	NS	11AM	11PM	15.8	TINGLING	6	6	1	Y	Y	N

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The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 31.08.2018 has approved the plan of thesis of Gaurav Bhatia, a student of your college for MCh Plastic & Reconstructive Surgery along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Comparison of bupivacaine moistened dressings and conventional dressings for donor site pain relief

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S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
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COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MCh IN

PLASTIC SURGERY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

February, 2018

DR GAURAV BHATIA

DEPARTMENT OF PLASTIC SURGERY (SPECIALITY)
DAYANAND MEDICAL COLLEGE & HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF
For the degree of	MCh IN PLASTIC SURGERY
Name of the candidate	Dr Gaurav Bhatia
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Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Skin grafting is one of most commonly done plastic surgery procedure. A split thickness skin graft harvesting creates a new partial thickness wound called the donor site. Donor site pain is one of the most distressing symptoms reported by patients in the early postoperative period. This study evaluates an effective pain relief method without any significant adverse effects.

Aim of Study: To compare the efficacy of 0.125 % bupivacaine moistened dressing and conventional dressing for pain relief on skin graft donor sites and to report any adverse effects.

Materials & methods: This randomized, prospective, comparative study will be conducted at Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital. The patients will be randomly divided into two groups with 30 cases in each group. Random number table will be used for this purpose. Group A will include patients with 0.125% bupivacaine moistened dressings. Group B will comprise of patients in which saline dressing will be used.

Patients will be interviewed for pain using Visual Analogue Scale every 8 hours by independent observer. Patients with complains of pain or in whom pain score was more than 4 (i.e. need for analgesia), will be given intravenous (IV) analgesia in the form of tramadol. Final conclusion of analgesia sparing effect of dressings will be made at 24 hours postoperatively and any side effect will also be noted.

Clinical Significance: This will lead to the development of simple and effective way for pain relief at the donor site.

Keywords: visual analogue scale, donor site

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Co-Supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF"** exist in the Department of plastic surgery, DMCH Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

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Topic of Thesis	COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF
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Approved: Yes / ~~No~~

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BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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4	DATE OF ADMISSION OF COURSE	21 OCTOBER 2017
5	TITLE OF THE TOPIC	COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Skin grafting is the most commonly done surgical procedure for soft tissue defects. Its wide range of applications make it valuable not only to plastic and reconstructive surgeons but also to other surgical specialties.[1]

A split thickness skin graft, consisting of epidermis and superficial dermis, is harvested from a remote area of healthy skin and is transferred to the wound. Harvesting split-thickness skin is the most common surgical procedure in managing burn injuries and this creates a new partial thickness wound with some dermal appendages intact. This is called the donor site.[2]

Split thickness skin grafts are used in most burns, reconstructive procedures and extensive wound management.[1] They are used to resurface large wounds, line cavities, re-surface mucosal deficits, close donor sites of flaps, re-surface muscle flaps and to cover tissue loss across joints in areas where contraction will cause deformity.[3] They are also used to achieve temporary closure of wounds created by the removal of lesions that require pathologic examination prior to definitive reconstruction.[4]

The grafting can reduce the course of treatment needed (and time in the hospital) as well as improve the function and appearance of the area of the body which receives the skin graft.[5]

Although STSG is the standard of care for full thickness burn wounds, complications, such as impaired healing, infection, excessive pain, scarring, pruritus, and either hypopigmentation or hyperpigmentation, are common on the donor site.[6] Since 1999, veteran's health administration has called for regularly documenting donor site pain as a "fifth vital sign." [7] Donor site pain

is also one of the most distressing symptoms reported by patients in the early postoperative period.[8] Larger donor sites stimulate a greater number of pain receptors and consequently pain is proportional to the size of the graft harvested.[9]

Often, the donor site is reported to be more painful than the recipient site, affecting early mobilization, sleep, and need for analgesics postoperatively.[10] Donor site pain is also a significant stressor during hospitalization and uncontrolled pain in the acute setting is a predictor of developing chronic pain in burn patients. [11,12]

There are many products available to cover donor sites. These include fine mesh gauze impregnated with petroleum jelly, polyurethane semipermeable transparent films, hydrocolloids and fibers like calcium alginate.[12] Despite an abundance of literature on wound dressings, no consensus has been reached on dressings that optimize management of postharvest donor site pain.[13]

Bupivacaine is an anesthetic agent that blocks the nerve impulses that transmit pain sensation to brain. It is most commonly used for spinal blocks but can also be used for local infiltration anesthesia and peripheral nerve blocks.[14] Thus, we planned this study to evaluate the role of bupivacaine moistened dressing in reducing donor site pain in comparison with saline soaked dressing.

6.2 REVIEW OF LITERATURE

Ideal donor site dressings do not interfere with healing, protect the wound from exogenous microorganisms, permit gas and fluid exchange, and are comfortable for the patient.[15]

In his meta-analysis, Wiechula compared moist dressings to nonmoist dressings. He evaluated 58 RCTs and intra individual studies where the efficacy of the dressing was determined by documenting signs of infection, effect on healing, and VAS scores. He found moist dressings decreased days needed for healing and were associated with decreased infection and lower pain scores. When comparing differences between moist dressings, he found hydrocolloids superior to other moist dressings in wound healing and infection. He did, however, find that pooling of results was challenging because a variety of pain measurements were used.[12]

Voineskos et al. reassessed moist versus non moist dressings by evaluating 75 studies for the same parameters (infection, wound healing, pain). In contrast to Wiechula, Voineskos et al. did not find evidence supporting moist dressings for reducing infection rate. Eleven studies favored moist dressings, five favored nonmoist, and 14 studies found no differences in wound healing. No dressing category or type was found to be superior. Pain scores were recorded in 58 of the 72 articles and a significant majority used VAS. Regardless of study design and consistent with Wiechula's review, majority of moist dressings were associated with less pain. Voineskos did, however, report that studies reviewed were of low methodological quality. Ultimately, there was a lack of definitive evidence favoring a particular dressing. Voineskos et al. suggested that future studies should clearly define their

experimental parameters and assess outcomes on more standardized scales.[13]

Dornseifer and colleagues enrolled 50 patients in a double-blinded randomised control trial where half of each donor site received silver impregnated hydrofiber and the other half received polyurethane dressings. An outer dressing hid the dressings under investigation until POD 10. Patients rated pain for each half of the donor site and healing was considered complete when no exudates was present and no pain was experienced upon exposure to antiseptic solution. The authors found that polyurethane dressings were associated with significantly decreased pain and faster reepithelialization.[15]

In a prospective study in Thailand by Jenwitheesuk et al, Forty patients without previous history of local anesthetic allergy and requiring split-thickness skin graft for reconstruction of various defects were studied. The patients were randomly divided into two groups. Group A received bupivacaine moistened dressing with 0.5% bupivacaine hydrochloride 6 m1/100 cm^2 instilled via catheter every 12 hours under aseptic technique. Group B, a control group, received saline moistened dressing with saline 6 m1/100 cm^2 instilled in the same method and intervals. In this study, bupivacaine soaked dressing was found to be significantly more effective in pain relief at donor site in early postoperative period with $p < 0.001$ in first four postoperative days and $p < 0.05$ on the fifth day.[16]

In another study performed in Nigeria, Oluwatosin and colleagues also used 0.5% aqueous solution of bupivacaine hydrochloride to treat the split thickness skin graft donor site. In this study, it was found that the patients in

whom donor site was treated with bupivacaine solution had significantly less pain compared to those in whom donor site was not treated with any solution, with $p < 0.00001$ on the first and second postoperative days, $p < 0.0005$ on the third and fourth day and $p < 0.0013$ on the fifth day.[17]

Muhammad Raza et al conducted a study including One hundred and fifty patients requiring split thickness skin grafting for various soft tissue defects and divided them into two groups A and B, with 75 patients in each group. In Group A, skin graft donor site dressing was kept moist with 12 mL/100 cm2 of 0.25% bupivacaine solution and in Group B, dressing was moistened with same amount of normal saline. Outcome was measured by calculating rescue analgesia requirements in the two groups after 24 hours. There was 93.3% effectiveness of bupivacaine soaked dressing while only 4% effectiveness of conventional dressing. They concluded that Bupivacaine soaked dressing is much more effective in pain relief and in reducing the requirement of rescue analgesia, in early postoperative period, at split thickness skin graft donor site compared to the conventional dressing.[18]

Butler and colleagues performed a prospective, double-blinded controlled trial with 45 patients split into three groups: (1) dry calcium sodium alginate dressing, (2) calcium sodium alginate dressing moistened in saline, and (3) calcium sodium alginate moistened with bupivacaine (0.5%). The method of pain assessment was not reported, but pain was assessed on POD 1, 2, and 3. Pain was reported to be significantly lower on POD 1 and 2 for patients receiving bupivacaine.[19]

In a study by Kadar and Obaid, the topical effects of bupivacaine post-tonsillectomy in tonsillar fossa in 70 cases was studied. The mean

postoperative pain scores for the subject fossae after 4 hours, before bed, before breakfast, before lunch and before discharge were less than control fossae scores, showing better pain relief with bupivacaine.[20]

Zohar et al. from Tel Aviv University studied the role of bupivacaine for pain relief in 36 patients after total abdominal hysterectomy and bilateral salpingooophorectomy. They divided patients in two groups. In one group (G1), they instilled 0.25% bupivacaine solution and in second group (G2), they instilled sterile water. When compared G1 required significantly less rescue analgesia ($p < 0.001$) than G2.[21]

In a study by Goldstein et al from Paris, the role of local anesthetics in preventing postoperative pain after laparoscopic gynecologic surgery was studied. In each patient, the operating surgeon instilled 20 ml of either 0.5% bupivacaine solution, 0.75% ropivacaine solution or normal saline depending upon the group. It was found that analgesia (morphine) requirement was considerably less in bupivacaine group than normal saline group ($p < 0.05$).[22]

Chester et al. published their study consisting of thirty consecutive patients undergoing cholecystectomy. The patients were randomised to receive continuous postoperative wound perfusion with 0.5% bupivacaine for 24 h followed by normal saline for a further 24 h or vice versa. During the study period, conventional analgesia was provided using a patient controlled analgesic device(PCAD) set to deliver (and record the number of) on-demand bolus doses of intravenous pethidine 0.2 mg/kg at half-hourly intervals as required. Pethidine requirements were higher on the first postoperative day, regardless of which solution was given, but bupivacaine perfusion almost halved mean linear analogue pain scores compared to those recorded with

saline. Likewise, the number of bolus doses of pethidine demanded was reduced by an average of 68% compared to those recorded during saline perfusion on day 1 (P = 0.01) and by 82% on day 2 (P = 0.01). When assessed by objective criteria, perfusion of surgical wounds with bupivacaine after cholecystectomy produces better pain relief than wound perfusion with saline.[23]

All these studies have proven that bupivacaine solutions are effective when used topically as instillation or as soakage of dressing on wounds to provide analgesia.

Other local anesthetic agents both short acting as well as long acting have also been tried topically to reduce pain at split thickness skin graft donor sites by plastic surgeons mostly with good results. Cenetoglu et al. used topical lignocaine gel at split thickness skin graft donor site and found very encouraging results as far as the pain relief was concerned. The effect was of shorter duration since lignocaine is a short acting anesthetic agent though its onset of action is early.[24]

6.3 AIMS AND OBJECTIVES

1. To compare the efficacy of 0.125% bupivacaine moistened dressing and conventional dressing for pain relief on skin graft donor sites.
2. To report any adverse effects.

7.0 MATERIALS AND METHODS

7.1 Source of Data

All patients being admitted to Dayanand Medical College and Hospital, Ludhiana undergoing split thickness skin grafting and who are willing to be a part of the study, will be included in the study.

INCLUSION CRITERIA

- All patients undergoing split thickness skin grafting and willing to participate in study
- Donor site – thigh
- Age 10-60 years

EXCLUSION CRITERIA

- History of allergy to any local anaesthetic
- Any cardiac history

This randomized, prospective, comparative study will be conducted at Department of Plastic and Reconstructive Surgery, Dayanand Medical College and Hospital. The patients will be randomly divided into two groups with 30 cases in each group. Random number table will be used for this purpose. Group A will include patients with 0.125% bupivacaine moistened dressings. Group B will comprise of patients in which conventional dressing will be used.

In both the groups, split thickness skin grafts will be harvested. Once the desired amount of the graft is harvested, the donor site wound will be first assessed for its dimensions. Donor site will be covered with Vaseline gauze, which will then be covered by a thin layer of sterilized gauze, a catheter will be longitudinally placed on this layer of gauze on the wound which in turn will be

covered with abundant amount of sterilized gauzes and finally crepe bandage will be applied to prevent external contamination.

In Group A, the donor site dressing will be kept soaked by instilling an aqueous solution of 0.125 % bupivacaine hydrochloride through the catheter under all aseptic techniques. The amount instilled will depend on the size of the graft taken. For every 100 cm^2 of the donor site wound, 12 mL of bupivacaine solution will be instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

In Group B, the donor site dressing will be kept soaked by instilling normal saline through the catheter under all aseptic conditions. Just like Group A, in Group B for every 100 cm^2 of the donor site wound 12 mL of the normal saline will be instilled once immediately after the surgery and then repeated after 12 hours of the first instillation.

For the assessment of pain, patients will be interviewed for pain using Visual Analogue Scale every 8 hours by an independent observer. Patients with complains of pain or in whom pain score was more than 4 (i.e. need for analgesia), will be given intravenous (IV) analgesia in the form of tramadol.

Final conclusion of analgesia sparing effect of dressings will be made at 24 hours postoperatively and any side effect will also be noted.

DURATION OF STUDY/ NUMBER OF CASES: 30 in each group

OUTCOME: Pain assessment using VAS

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between

the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. A probability value (p value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY

Yes. The study requires instillation of normal saline and bupivacaine through the catheter for topical application.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith.

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PROFORMA

S. No.

MRD. No.

NAME

AGE/SEX

FATHER'S/HUSBAND'S NAME

CHIEF COMPLAINT:

HISTORY OF PRESENT ILLNESS:

PAST HISTORY:

H/O allergy to Local Anaesthetics:

Associated Illness:

WOUND HISTORY:

Mode of onset

Duration

TYPE OF ANESTHESIA:

DONOR SITE:

DONOR AREA DIMENSIONS:

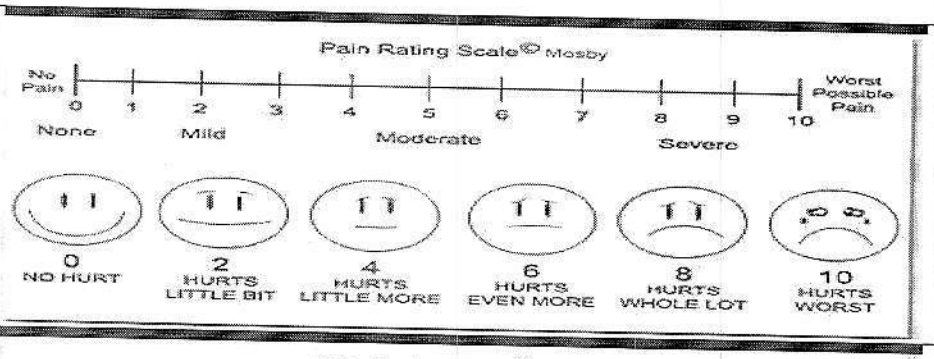
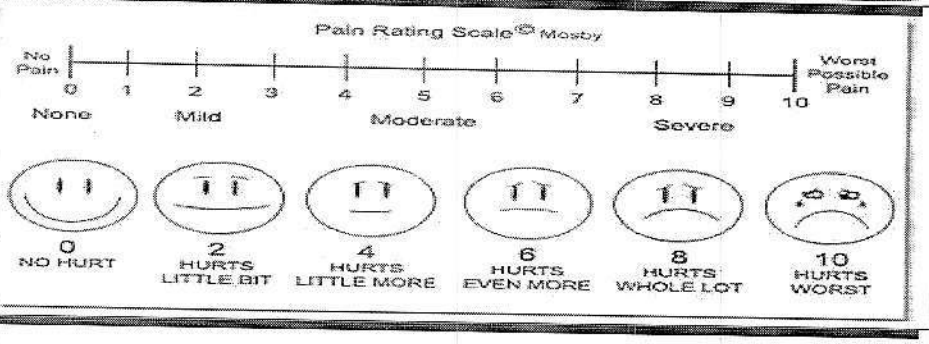
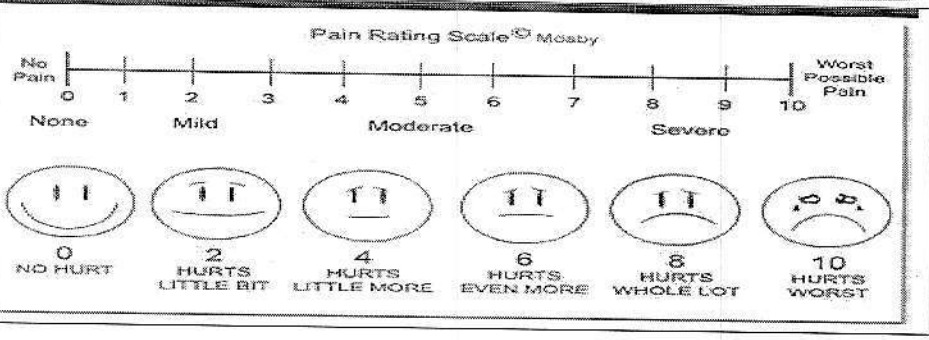
TIMING OF BUPIVACAINE/NORMAL SALINE INSTILLATION

dose	time	quantity	Adverse effect
1st			
After 12 hours			

Signature of candidate

Signature of supervisor

PAIN SCORE

	VAS score	Need for pain relief/drug administered
8 hours		
16 hours		
24 hours		

Final assessment at 24 hours:

Signature of candidate **Signature of supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

am willing to participate in the study **"COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____ निवासी _____ इस शोधकार्य "**COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____
गवाह के हस्ताक्षर
नाम:

_____
रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:

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अन्वेषक के हस्ताक्षर

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विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫ਼ਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"COMPARISON OF BUPIVACAINE MOISTENED DRESSINGS AND CONVENTIONAL DRESSINGS FOR DONOR SITE PAIN RELIEF" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ